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EDITORS
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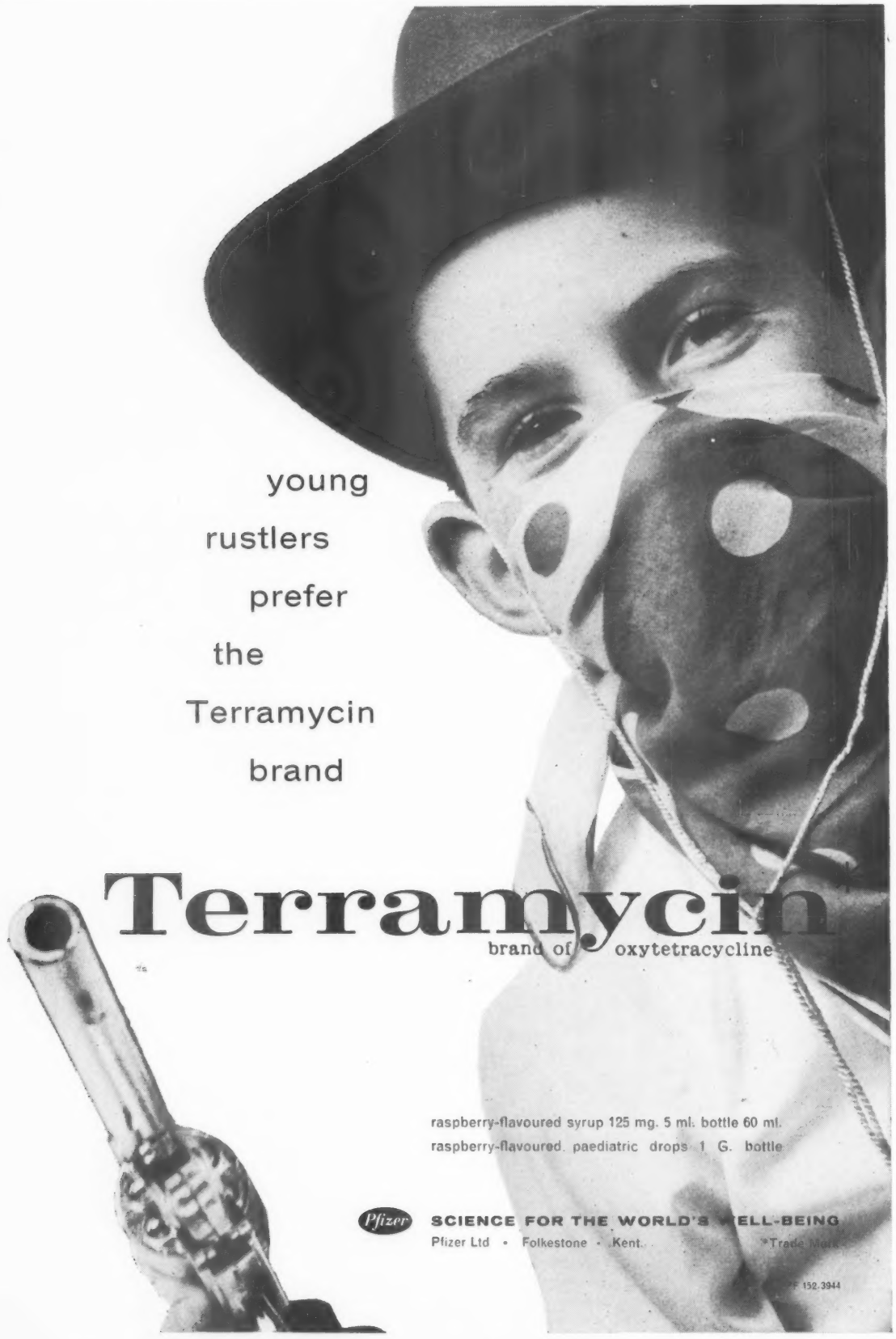
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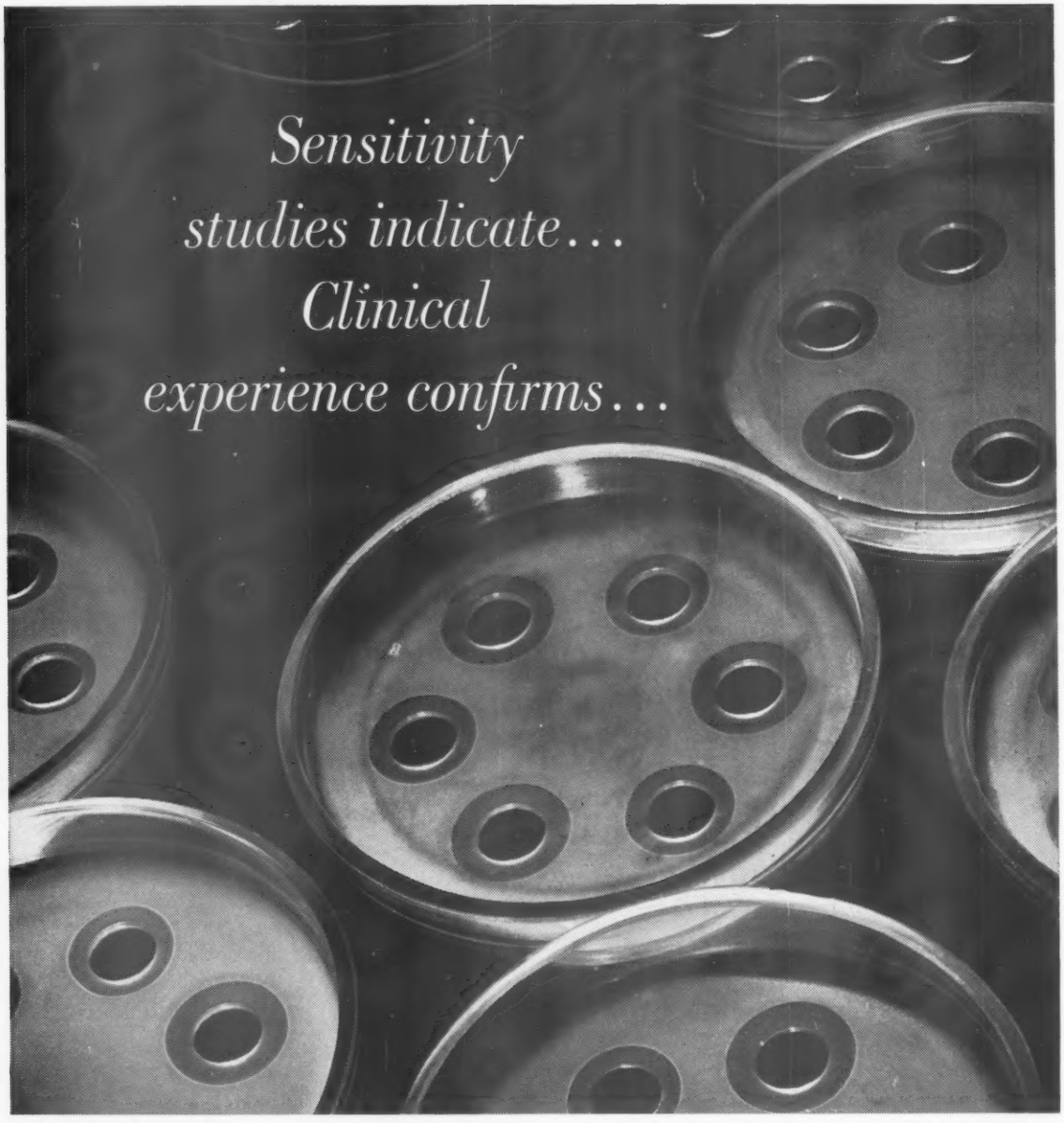

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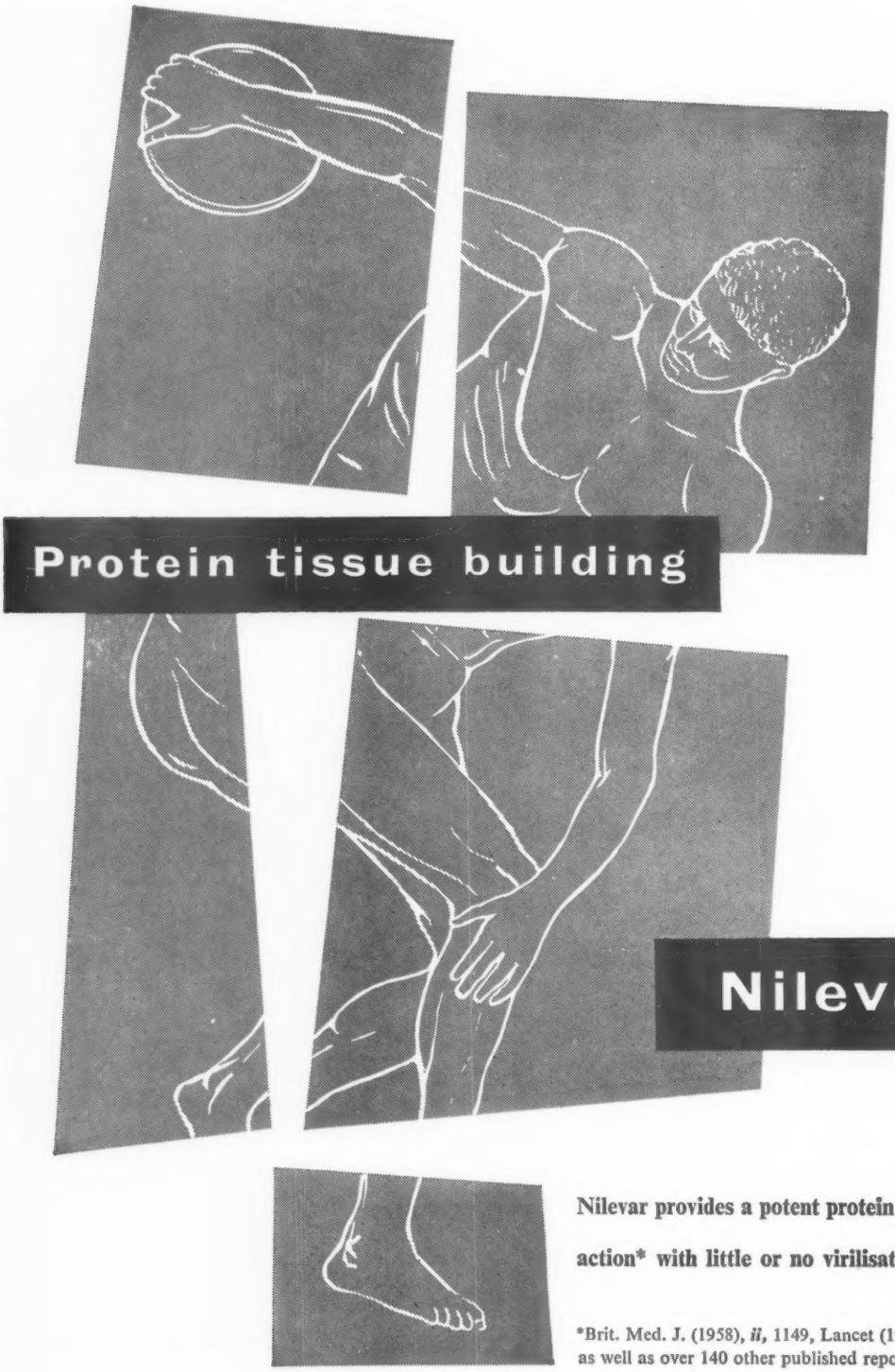

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HISTOLOGICAL CHANGES IN THE DUODENAL MUCOSA IN COELIAC DISEASE

REVERSIBILITY DURING TREATMENT WITH A WHEAT GLUTEN FREE DIET

BY

CHARLOTTE M. ANDERSON

From The Royal Children's Hospital, Melbourne

(RECEIVED FOR PUBLICATION JUNE 23, 1960)

From the examination of biopsy material Sakula and Shiner (1957), Rubin, Brandborg, Phelps and Taylor (1960a) have demonstrated histological changes in the duodenal mucosa of patients with coeliac disease or wheat gluten intolerance and shown that these changes are identical with those demonstrated by themselves and others in adult patients with idiopathic steatorrhoea. The changes recorded by all observers in both conditions are very similar but vary in severity in individual patients. However, the interpretation of the nature of these changes and whether they are primary anatomical ones or secondary to the effect of ingested food substances has not been clearly demonstrated and is still a matter for conjecture.

Shiner and Doniach (1960) in their most recent publication state that the histology suggests defective formation of villous epithelial cells and describe the picture as villous atrophy of varying grades. They suggest that the changes are primary and irreversible and the harmful effect of wheat gluten is superimposed on this primary atrophy. Rubin, Brandborg, Phelps, Taylor, Murray, Steimler, Howry and Volwiler (1960b) also suggest that the lesion is an irreversible one and that it may persist throughout life; they agree, however, that their evidence for this is incomplete, as in two patients the lesion appeared to improve with treatment.

The present study demonstrates the histological changes in the duodenal mucosa in biopsy material from a group of newly diagnosed young coeliac patients and the complete or partial disappearance of these changes during the first year of treatment in patients of this group from whom subsequent biopsies have already been obtained.

Material and Method

Clinical Material. From January, 1959 to April, 1960, a single duodenal mucosal biopsy was obtained from each of 17 children newly diagnosed as cases of coeliac disease or wheat gluten intolerance. All children were subsequently treated by excluding wheat gluten from the diet and were followed carefully. In 11 of these patients biopsies have been repeated at certain intervals during treatment.

Criteria for initial diagnosis were rigid and only children showing the features of clinical history and physical examination recorded in previous publications (Anderson, Frazer, French, Gerrard, Sammons and Smellie, 1952b; Anderson, 1959) were included. Laboratory investigations demonstrated steatorrhoea by fat balance, normal quantities of pancreatic enzymes in duodenal fluid using the methods described previously (Anderson *et al.*, 1952b), normal sodium and chloride content of sweat determined by the method of Anderson and Freeman (1958). Gastro-intestinal infection and tuberculosis were excluded by relevant tests. All patients improved rapidly and showed normal clinical progress on a wheat gluten free diet.

During the period of treatment the diet was carefully checked at each visit. At the time of each subsequent biopsy, a three-day stool collection was examined for total fat excretion; haemoglobin, weight, height and clinical progress were recorded.

Collection of Biopsy Material. Biopsies were obtained by the multipurpose suction biopsy tube of Brandborg, Rubin and Quinton (1959) without the mercury containing balloon attached. Patients were fasted overnight and the tube passed orally while the patient was under basal anaesthesia with rectal bromethol (100 mg./kg.). The end of the tube was manoeuvred into the duodenum under fluoroscopy using an image intensifier and television screen. Radiation table dose was between 0·5 and 1 roentgen in young children and did not exceed 2 roentgens in the older children; the procedure was abandoned after these levels had been reached, if the tube was not in position. Specimens were taken from the second, third or fourth part of the duodenum and were about 3-5 mm. in diameter, consisting of mucosa and muscularis mucosae with a minimum of submucous tissue.

It has not been found easy with this type of tube, within the limits of radiation dosage and with the tube passed by mouth instead of nose, to obtain specimens beyond the duodenojejunal flexure in young children. Therefore in this paper the duodenal mucosal changes only are described.

No post-biopsy complications were encountered. The use of basal anaesthesia helped in the ease of the procedure and in abolishing any unpleasant memories of the event from the minds of the children, allowing follow-up material to be obtained more readily. A single biopsy specimen only from each child was examined as success in obtaining more than one specimen at a time was very limited.

The method for orientation of the biopsy specimens, fixing and H. and E. staining followed substantially those described by Rubin *et al.* (1960a) and, as these authors recommend, sections from the central core of the specimens were examined to avoid tangential artefacts. The sections were examined, and compared with reference to particular features by the author, who was aware of their origin and also by two pathologists of the Royal Children's Hospital, Melbourne, Dr. A. Williams and Dr. L. Taft, independently, and without knowledge of their origin. Quantitative counting of villi as described by Rubin *et al.* (1960a) was not carried out.

Duodenal biopsies from children without organic disease have been obtained under identical conditions and examined in the same way. The appearance described by Shiner and Doniach (1960) and Rubin *et al.* (1960a) for normal duodenum have been confirmed, but for the sake of brevity are not illustrated again in this paper.

Results

Initial Biopsy Specimens. The duodenal mucosa was abnormal in all patients. Low magnification microscopic examination showed a characteristically flat surface to the mucous membrane. In most cases villi were completely absent, replaced by broad flat areas between crypts (Figs. 1, 3, 7 and 11). In a few, flattened stumpy villi were present but these did not show branching nor project above the surface (Fig. 2). The chief characteristic was the straight flat edge of the mucosal surface. In the majority, surface epithelial cells were altered, the single layer of tall columnar cells with basal nuclei being replaced by flattened cells with irregularly placed nuclei, sometimes several layers of cells giving a stratified appearance. Usually very few goblet cells were present on the surface, but in the crypts epithelial cells had a more normal appearance and goblet cells were present. The lamina propria was considered of normal thickness but in some cases a deceptive increase in thickness was suggested because the lamina was not drawn up into the villi. The lamina propria contained many plasma cells, some eosinophils and occasional polymorphonuclear cells, but there was considerable variation in the density of cell population among individual cases, this being often about the upper limits of normal, but sometimes greater than normal.

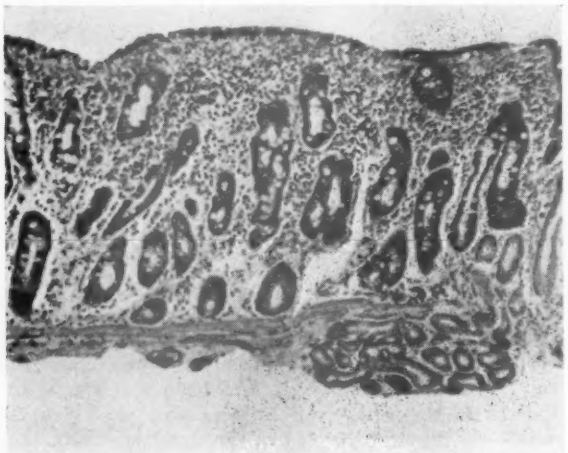

FIG. 1.—Example of duodenal biopsy (× 37) from Group I. Case 5—moderately severe (+++) changes—long flat areas between crypts—irregularity of surface epithelium.

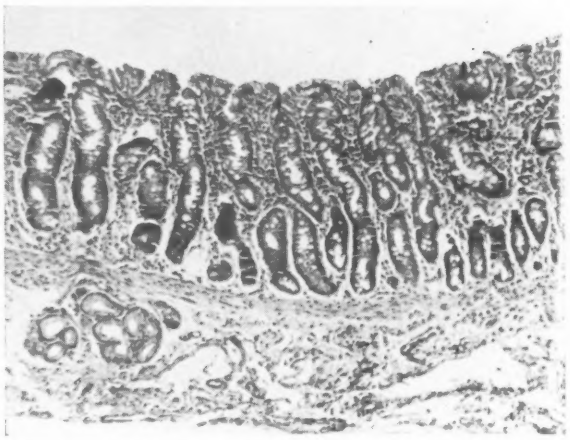

FIG. 2.—Example of duodenal biopsy (× 35) from Group II. Case 14—straight edge to mucosal surface—short stumpy villi—minimal change in epithelial cells.

As only one biopsy specimen was obtained from each patient a strict quantitative assessment of the mucosal changes seemed unwise since it is probable that these changes vary from place to place in the gut. However, the biopsies did show individual variation and the degree of severity of the changes was rated according to a series of pluses (+), by the three observers, independently, with very minor disagreement. In Table 1 this rating is compared with certain clinical findings. Only the most characteristic features were considered in determining the rating; for instance, degree of

TABLE 1

CLINICAL FINDINGS IN 17 CASES OF COELIAC DISEASE COMPARED WITH SEVERITY OF DUODENAL MUCOSAL CHANGES IN BIOPSY SPECIMENS

Case No.	Sex	Age in Years	Approximate Duration of Symptoms	Weight (kg.)	Hb g./100 ml.	Fat Excretion (g./day). Average 5 days	Severity of Histological Changes in Duodenal Mucosa
Group I							
1	F	1 year 6 mths	4 mths	10	10	9	++++
2	F	1 year 8 mths	8 mths	8·2	9·9	10·1	++++
3	M	10 years 1 mth	Years	32	14·1	16·3	++++
4	M	10 years	Years	24	11·5	13·5	++++
5	F	1 year 6 mths	2 mths	10	10	17	+++
6	M	4 years 5 mths	3 years	15	8·4	30·4	+++
7	M	6 years 8 mths	Years	18	9	10·4	+++
8	M	4 years 11 mths	Years	18	10·1	19	+++
9	F	9 mths	3 mths	9	12·1	9·4	+++
10	F	1 year 10 mths	2 mths	10·6	11·5	30·0	+++
11	M	1 year 2 mths	1 mth	7·5	10·1	6·4	+++
Group II							
12	M	6 years 4 mths	Years	14·5	13·5	14·8	++
13	M	1 year	3 mths	8·5	10	6·5	++
14	M	1 year 9 mths	Mths	9	9	11·5	++
15	F	2 years 11 mths	Mths	12·6	9	19·6	++
16	F	1 year 9 mths	2 mths	7·7	10	12·7	+
17	F	2 years	Mths	10	9·3	8·8	+

++++ Most severe—disorganization of surface epithelium with stratification, no villi.
+++ Occasional flattened villi, otherwise as above.
++ Surface epithelium less severely disorganized, no stratification. Occasional flattened villi.
+ Least severe, surface epithelium still tall columnar with some flattened areas. Villi stumpy and poorly differentiated from crypts. Straight edge to mucosa.

TABLE 2

CLINICAL FINDINGS IN 11 TREATED CASES OF COELIAC DISEASE (FROM TABLE 1) AND DEGREE OF IMPROVEMENT IN DUODENAL BIOPSY

Case No.	Duration of Treatment	Strictness of Diet	Weight (kg.)	Hb g./100 ml.	Fat Excretion (g./day)	Biopsy—Degree of Improvement
1	0	Very occasional lapse	10	10	9	—
	9 mths		13	13	5·3	++
2	0	Occasional lapse	9·9	8·2	10·1	—
	9 mths		12·0	11·8	3·2	++
5	0	Strict	10	10	17	—
	9 mths		17	11·3	6·6	+
6	0	Very occasional lapse	15	8·4	30·4	—
	3 mths		18	9	5·6	++
	12 mths		20	11	6·5	+++
7	0	Strict	18	9	10·4	—
	3 mths		20·4	10·1	5·2	++
	11 mths		22	11·5	6·3	+++
8	0	Took other children's food occasionally	18	10·1	19	—
	11 mths		22	12·3	11·7	+++
10	0	One cake just before second biopsy	10·6	9·5	30	—
	3 mths		15	11·7	11	+++
11	0	Strict	7·5	10·1	6·4	—
	3 mths		8·5	11·3	2·4	+++
12	0	Strict	14·5	13·5	14·8	—
	3 mths		17·2	12·3	3·8	++
13	0	Strict	8·5	10·0	6·5	—
	3 mths		10·8	11·8	1·5	+
14	0	Only fair supervision	7·7	10·0	12·7	—
	11 mths		10·7	—	5·1	++

\+ Villi present but still stumpy, surface epithelium tall columnar cells.
++ Villi longer but not quite normal, surface epithelium normal.
+++ Villi and surface epithelium within normal limits.
Fat Excretion. Initial: Average of five days. In-patient.
Follow-up: Average of three days. Usually out-patient.
Diet: As far as could be assessed by comprehensive questioning of mother.

disorganization of surface epithelium and state of the villi.

Table 1 shows that the cases fall into two groups, the first 11 in whom the changes were severe or moderately severe, and the remaining six in whom the changes were definitely milder, particularly the change in surface epithelium. The majority of the older children and therefore those in whom

symptoms had been present for the longest time, are in the first group. However, this correlation is not complete as there is one older child with mild changes (Case 12) and two quite young children (Cases 1 and 2) with very severe (++++) changes. Among the first group the degree of malabsorption in most cases appears to be rather more severe than in the second group but this correlation is still not extremely close, Cases 12 and 15 showing moderately severe malabsorption and Cases 1, 9 and 11 showing a milder degree of malabsorption. The degree of clinical illness did not correlate with the changes, as some of the very young children of the second group showed quite severe symptoms, whereas the older children in the first group showed milder clinical symptoms which no doubt accounted for their late diagnosis. The two 10-year-old boys had been diagnosed in early infancy, treated for one or two years, and had then resumed a normal diet and were considered fairly well until readmitted for investigation of recurrent abdominal pain.

Biopsy Specimens During Treatment. In Table 2 the patients from Table 1 who had biopsies repeated during treatment are listed with records of fat excretion, haemoglobin and weight gain at those stages, together with some indication of the degree of improvement in the appearance of the mucosa. In all cases alteration and improvement towards normal were noted, but to a variable degree, resumption of a normal or near normal appearance of the surface epithelial cells being the most constant and marked feature. Tall columnar cells interspersed with goblet cells are again present. Villi reappeared in each case but were very variable in their size, shape and number. Again a rating has been given to each of the subsequent biopsies, according to the degree of improvement in the surface epithelium and the villi. In five (+++) the biopsies were considered to be within normal limits; in four (++) the surface epithelium was normal in appearance but the villi were considered to be still somewhat shorter and wider than normal. In two the improvement was slight (+) villi being very short and blunted but there was definite improvement in the appearance of the surface epithelium which was of the normal tall columnar type. The degree of improvement did not correlate well with any particular clinical feature, but was present after three months' treatment (Cases 10 and 12) to a similar extent, as after nine to 12 months' treatment (Cases 6 and 7).

Dietary restriction was well carried out but in most patients occasional lapses took place, more particularly in the school age children who accepted offerings from schoolmates, or because the mother was unaware that certain prepared and tinned foods contained gluten. Absorption was not always quite normal when the biopsies were repeated and these dietary lapses may have contributed to this. Marked clinical improvement had taken place in each case as can be seen from the weight and haemoglobin gains, but the biopsy did not always show a comparable degree of improvement.

Figs. 3 to 14 give visual evidence of the improvement in three patients. Low magnification pictures show the overall appearance of the biopsy with reappearance of villi during treatment, and higher magnification illustrates the detail of epithelial cells and lamina propria. Figs. 3 to 6, from Case 6, illustrate the return to a normal or near normal appearance in the specimen taken 12 months after the beginning of treatment. Figs. 7 to 10, from Case 10, illustrate biopsies taken initially and after only three months of treatment and show a return to normal appearance of villi and surface epithelium. Figs. 11 to 14 from Case 1 illustrate a lesser degree of improvement of the villi, despite good clinical improvement, strict dietary regime and normal absorption; initial changes were of the severe type (++++) with complete absence of villi and gross alteration of surface epithelial cells.

Discussion

Histological changes in the duodenal mucosa of patients with coeliac disease investigated in this study appear to be identical with those recorded by Sakula and Shiner (1957) and Rubin *et al.* (1960a). The variation in severity of the changes in the initial biopsy specimens parallels closely that observed by Rubin *et al.* (1960b) and the present findings agree with theirs, in that little correlation occurs between the severity of the lesion and the clinical symptoms; somewhat more correlation occurs with the degree of malabsorption; the closest degree of correlation is with the age of the patient. The most severe lesions occurred in the older children although again there were exceptions.

Changes in the mucosa of the small intestine in patients with coeliac disease and idiopathic steatorrhoea indicate a reduction in surface area exposed to digested foodstuffs and this is thought to be responsible for malabsorption. In the present study some of the patients with severe degree of malabsorption, as determined by fat balance, did show the most severe changes in histology of the duodenal mucosa. However, some of the children with milder lesions showed considerable malabsorption (Cases 12 and 15). Explanation of this is uncertain but only one biopsy

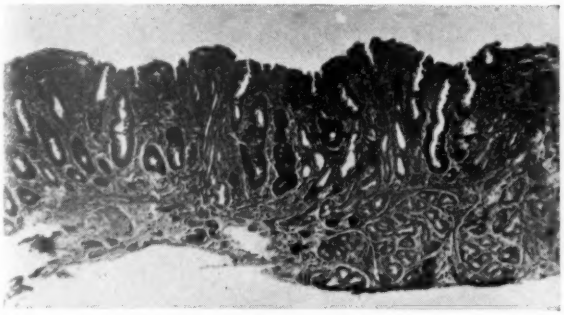

FIG. 3.—Initial biopsy (×31).

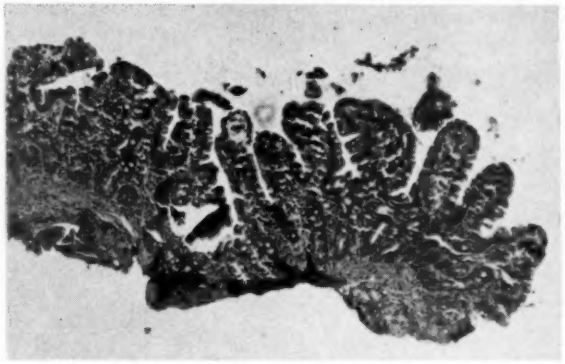

FIG. 4.—Biopsy after 12 months' treatment (× 33).

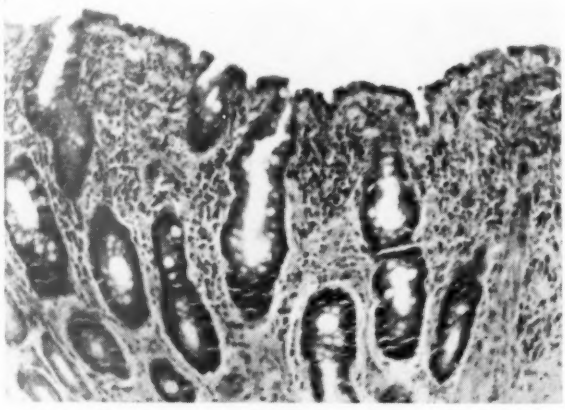

FIG. 5.—Initial biopsy (× 85).

FIG. 6.—Biopsy after 12 months' treatment (× 86).

FIGS. 3–6.—Case 6—illustrating improvement (+++) in duodenal biopsy specimen after 12 months' treatment with gluten-free diet. Normal appearance of villi and epithelial cells.

from each patient has been examined and the changes in the rest of the mucosa may have varied as shown by Rubin *et al.* (1960a). That clinical symptoms did not parallel biopsy changes is not so surprising since the degree of malabsorption does not always parallel severity of clinical symptoms. Observation of patients with coeliac disease during a number of years has shown that this latter finding is a common one. It is also characteristic that symptoms in later childhood may not be as severe as in early life, despite an apparently greater absorptive defect. This was clearly seen in Cases 3 and 4, two boys of 10 years, who were thought to have recovered from childhood coeliac disease and were taking a normal diet. Their absorptive defect was considerable despite only mild symptoms of recurrent abdominal pain, recurrent loose stools in one and constipation in the other. The author holds the view that the degree of malabsorption in coeliac disease does not fully explain the degree of illness nor malnutrition and that there is probably some generalized deleterious effect of the toxic fraction of wheat gluten, this effect being more serious in the young child.

In the present series mucosal changes in the biopsies obtained during the patient's treatment with a wheat gluten-free diet have altered, and a more normal and sometimes quite normal appearance is resumed. The improvement is consistent in type although variable in degree. This finding is at variance with that of Sakula and Shiner (1957), who report one case of coeliac disease, stating that improvement in mucosal histology did not occur after five weeks' treatment. However, they give no detail of the rigidity of the gluten-free diet, nor the state of absorption at the time of the second biopsy. Rubin *et al.* (1960b), in their most recent communication, report two patients in whom they considered some improvement had taken place on a gluten-free regime, although they did not

FIG. 7.—Initial biopsy (× 31).

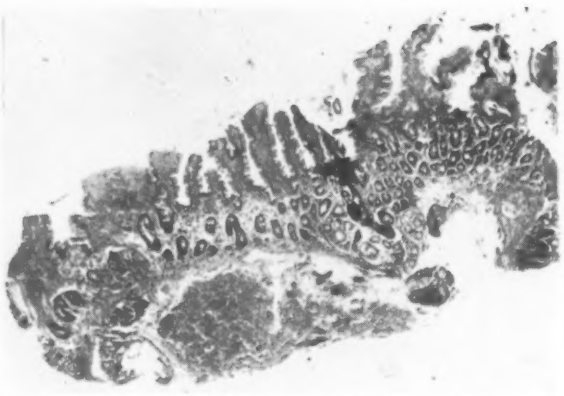

FIG. 8.—Biopsy after three months' treatment (×29).

FIG. 9.—Initial biopsy (× 86).

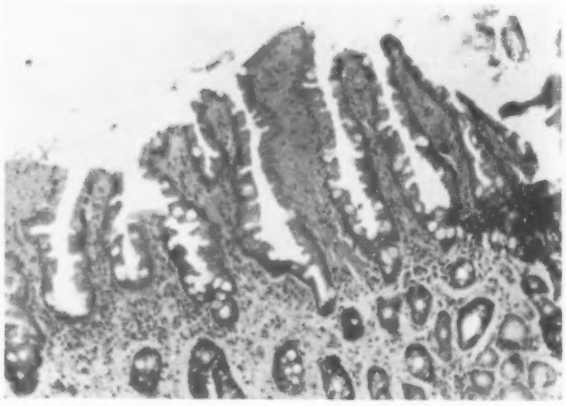

FIG. 10.—Biopsy after three months' treatment (× 86).

FIGS. 7–10.—Case 10—illustrating improvement (+++) in duodenal biopsy specimen after three months' treatment with gluten-free diet. Normal appearance of villi and epithelial cells.

discard the view that the histological lesion was a primary one, because other patients did not show such improvement.

Single biopsies only have been examined in the present study, the state of the rest of the small intestine at the time being unknown. It is perhaps unwise to make a dogmatic conclusion from this type of material but the fact that all the patients who were followed showed some degree of improvement in histology of the mucosa is enough evidence to conclude that the lesion is at least associated with the presence of wheat gluten in the diet.

The degree of improvement varied considerably, some subsequent biopsies being normal, others showing moderate improvement, others still less. However, all showed a surface epithelial cell which looked normal, in that it was tall columnar with a basal nucleus. Variation showed up particularly in the size, shape and number of villi. Interpretation of what is normal in this respect is difficult, as mentioned by Shiner and Doniach (1960) and observed by ourselves in controls. The fact that there can therefore be considerable variation in size, shape and number of villi in patients with normal intestinal absorption makes it not impossible that some coeliac patients may have normal or near normal absorption without completely normal villi. Moreover, in man, the small intestine is certainly longer than is necessary for maximal absorption, since considerable lengths may be removed surgically without altering absorptive capacity. Consequently a complete return to normality in histological appearances of the duodenum is not necessary before the child can be clinically well and show normal absorption. The degree of improvement may be sufficient, or other

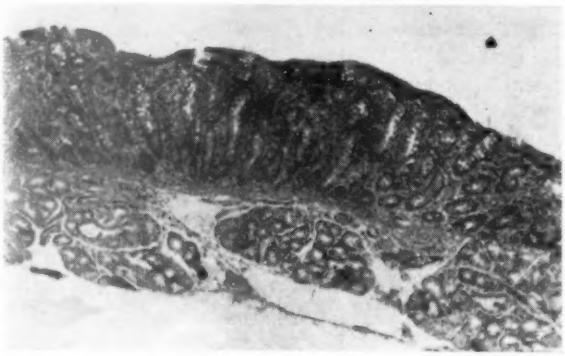

FIG. 11.—Initial biopsy (× 28).

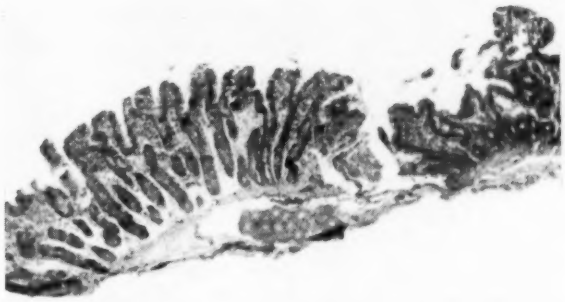

FIG. 12.—Biopsy after nine months' treatment (× 28).

FIG. 13.—Initial biopsy (× 86).

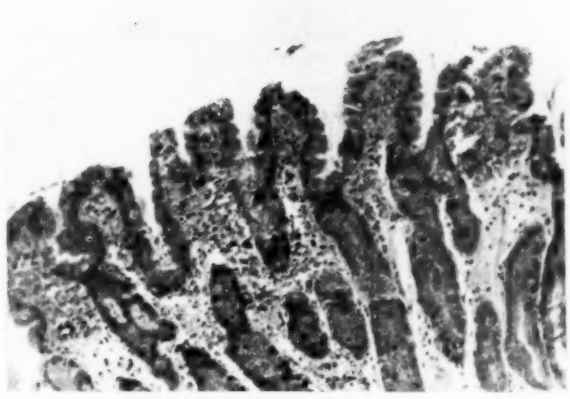

FIG. 14.—Biopsy after nine months' treatment (× 86).

FIGS. 11–14.—Case 1—example of most severe changes (++++) in initial duodenal biopsy specimen, and moderate (++) improvement after nine months' treatment with a gluten-free diet. Villi still short and stumpy—epithelial cells normal.

parts of the gut may have improved still more.

If the abnormal changes are directly associated with the presence of gluten in the diet, return to complete normality must also depend on the rigidity and persistence of the gluten-free dietary regime. Experience over a number of years has shown how difficult it is for active toddlers and school children to be accurately restricted in diet. The complexity and diversity of modern, prepared and tinned foods makes it difficult for a mother to know which foods contain gluten, often used as an additive. Until the toxic fraction of wheat gluten is recognized it will not be clearly known whether small amounts may occur in other foodstuffs, in amounts, for instance, too small to cause clinical symptoms but enough to prevent full normality of the mucosa. Rubin *et al.* (1960b) did not comment on the strictness of the diet in their patients who did not show improvement in duodenal histology, but it is perhaps significant that in the two patients who did show improvement, biopsies were obtained after only short periods of treatment. It is well known to those who treat these children that the diet is much more rigidly adhered to in the early stages of treatment than later when the child is well. The present study shows that improvement in histological appearances is evident quite early during treatment, even after only three months, at which time it may be as marked as after nine months.

From the data presented in this paper it can be seen that in very young coeliac patients who were kept as rigidly as possible to a wheat gluten-free dietary regime, the histological appearances of the duodenal mucosa improved significantly. Improvement was also noted in 6-year-old children who had had symptoms since toddler age. The two 10-year-old boys have not yet been re-investigated. The appearance of the mucosa in these older patients resembles the severity of change seen

in adult patients. It is well known that adult patients do not show such a quick response clinically to a gluten-free dietary regime as do young children (French, Hawkins and Smith, 1957). This may have some relationship to the fact that Rubin *et al.* (1960b) do not demonstrate significant improvement in biopsy specimens from older patients. Have the changes been present too long for much improvement in structure to take place, or will it take longer, or depend on the replacement of other long-standing deficiencies in these patients?

Interpretation of the mechanism of the deleterious effect of gluten on the duodenal mucosa is still a matter for conjecture and no real evidence for this is presented in this paper. Present theories of the toxic mechanism of gluten in coeliac disease postulate the production of a harmful peptide in the intestine due to incomplete proteolytic digestion of gluten (Weijers and Kamer, 1955; Frazer 1956; Alvey, Anderson and Freeman, 1957). If this is so, is this peptide directly irritative to the mucosal surface or is it absorbed, exerting its toxic influence generally on the patient and more particularly on the intestinal mucosa. Anderson, Astley, French and Gerrard (1952a) have shown from barium studies that the small intestine in coeliac disease is dilated and lacks the normal fine feathery patterning of the mucosa. They have suggested that this may be evidence of generalized loss of tone in the gut wall or that the muscularis mucosae is hypotonic. The dilatation disappears on recovery and reappears during relapse. It is well known that the young child with coeliac disease shows hypotonia of skeletal musculature out of proportion to the degree of malnutrition and that the child is temperamentally depressed. These features also disappear with treatment. It is possible that the harmful fraction of gluten may in some way cause hypotonia and that the effect of this on the gut is to depress the activity of smooth muscle and muscularis mucosae, perhaps altering the appearance of villi and mucosa. Verzar and McDougall (1936) have described and recorded the movements of the villi and their control by the muscularis mucosae. Johnson (1913) has shown, in animals, that when the small intestine is dilated the villi become shorter and blunter, the surface flatter and that alterations appear in the tall columnar cells. Is there villous atrophy as described by Shiner and Doniach (1960) or failure of formation of villi by alteration of villous mechanics?

It is possible that toxic influences other than gluten may produce similar changes in the gut and mucosa. Clinically and biochemically tropical sprue closely resembles adult idiopathic steatorrhoea and coeliac disease, but does not respond to a gluten-free dietary regime (French, *et al.*, 1957). Butterworth and Perez-Santiago (1958) among others, have reported similar changes in the intestinal mucosa in patients with tropical sprue but these are milder in nature, resembling the less severe cases in the present series, and they are apparently reversible. The gut in this condition also has the same dilated hypotonic appearance (Ardran, French and Mucklow, 1950). Shiner and Doniach (1960) have reported similar mild reversible changes in biopsy specimens from patients with post-gastrectomy steatorrhoea. Rubin *et al.* (1960a) show good evidence that this mucosal lesion is specific to coeliac disease and adult idiopathic steatorrhoea among the series of patients they investigated. The present study shows no evidence for or against the specificity of this lesion owing to inadequacy of material. However, biopsy material from children with other disturbances of gastro-intestinal function and motility, temporary as well as chronic, with or without associated malabsorption, must be studied before the specificity of this lesion, particularly in its milder grades, is unquestioned.

Summary

Histological changes in the duodenal mucosa in biopsy material obtained from 17 patients with newly-diagnosed coeliac disease are described. These changes are of a consistent pattern but vary in severity.

The abnormal changes disappeared completely or partially in biopsy specimens obtained from all 11 of these children who were followed during their first year of treatment with a diet free from wheat gluten.

The histological changes in the intestinal mucosa of patients with coeliac disease are considered to be directly associated with the ingestion of wheat gluten.

The histopathology of the lesion is briefly discussed.

Many people have helped in various phases of this work and to them I owe thanks: Dr. Rubin and his colleagues in Seattle for supplying me with an early model of the biopsy tube and personal instruction in the preparation of sections; the physicians of the Royal Children's Hospital for generously referring clinical material; the registrars, nursing staff and radiology staff who have helped in obtaining the biopsies; Miss Mavis Freeman and the Clinical Research Unit laboratory for the laboratory investigations; Miss Jean Allan for supervising the diets; the Pathology Department technicians for cutting and staining the sections; and lastly to the two pathologists, Dr. A. Williams and Dr. L. Taft, for reviewing the sections with me.

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Addendum

Since this paper has been sent to the press, Rubin, Brandborg, Flick, Parmentier, Phelps and Van Niel (1960) have demonstrated in two treated adult sprue patients that instillation of wheat into the ileum was followed by changes in the mucosa. These changes were those characteristic of the sprue lesion prior to treatment with a gluten-free diet. These authors state that this demonstration of intestinal mucosal damage by wheat implicates gluten exposure as the precursor to anatomic changes in idiopathic sprue.

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THE VALUE OF GALACTOSE PHOSPHATE DETERMINATIONS IN THE TREATMENT OF GALACTOSAEMIA

BY

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Hereditary galactosaemia is now known to be due to the deficiency of a single enzyme, galactose-1-phosphate uridyl transferase* (Kalckar, Anderson and Isselbacher, 1956). This enzyme, the second in the chain of three enzymes concerned with the metabolism of galactose, catalyses the conversion of gal-1-P to G-1-P, as shown in equation (2):

$$\text{gal} + \text{ATP} \rightarrow \text{gal-1-P} + \text{ADP} \quad (1)$$

$$\text{gal-1-P} + \text{UDPG} \rightleftharpoons \text{G-1-P} + \text{UDPgal} \quad (2)$$

$$\text{UDPgal} \rightleftharpoons \text{UDPG} \quad (3)$$

The block in galactose metabolism at step (2) would be expected to lead to an accumulation of gal-1-P when galactosaemic individuals ingest galactose. An accumulation of this phosphate has been demonstrated in the erythrocytes of untreated infants suffering from galactosaemia, or in the erythrocytes of treated cases after incubation with galactose *in vitro* (Schwarz, Golberg, Komrower and Holzel, 1956; Kalckar *et al.*, 1956). A diagnostic test for galactosaemia, based on this observation, has been reported previously (Schwarz, Holzel and Komrower, 1958).

The intracellular accumulation of gal-1-P appears to lead to a serious disturbance of erythrocyte metabolism, as indicated by a fall in the respiratory rate and by a general derangement of phosphate metabolism (Schwarz *et al.*, 1956; Komrower, Schwarz, Holzel and Golberg, 1956; Penington and Prankerd, 1958). An analogous disturbance has been demonstrated in a mutant of *E. coli* deficient in uridyltransferase: on incubation of the culture with galactose, it evinces a prolonged lag phase before the onset of growth, which is preceded by intracellular accumulation of gal-1-P (Kurahashi and Wahba, 1958). Recently evidence has been presented which indicates that gal-1-P may exert an inhibitory effect on a number of enzymes—phosphoglucomutase, G-6-P phosphatase and dehydrogenase (Sidbury, 1957; Ginsburg and Neufeld, 1957; Lerman, 1960).

So far gal-1-P has been demonstrated only in the erythrocytes of galactosaemic infants. The liver, being the main site at which galactose is normally metabolized, would be expected to show a similar, or even greater, accumulation of this phosphate. Theoretically, all cells of the body are endowed, to a greater or lesser extent, with all enzymes and a hereditary deficiency in one enzyme might therefore make itself felt in all tissues.

The purpose of this communication is threefold: to demonstrate that gal-1-P does, in fact, accumulate in several, if not all, tissues; to draw attention to the value of assessing erythrocyte gal-1-P at regular intervals as a guide to the adequacy of treatment; to present an improved method for the determination of gal-1-P.

The gal-1-P values reported below were obtained by the method published previously (Schwarz *et al.*, 1958). Since this method was evolved and most of the determinations made, pure gal-1-P has become available, thus permitting an assessment of the efficiency of its determination. Recent experiments have shown that the original method may involve losses of galactose resulting from irreversible adsorption on, or entrainment in, the salts left after evaporation to dryness. To overcome this defect as far as possible, and still retain the specificity of the method accruing from chromatographic separation of galactose from other carbohydrate or reducing substances, the following method has been devised.

Determination of Gal-1-P

Heparinized venous blood (about 2 ml.) which may be kept in ice (not frozen) for a few hours, is centrifuged

* The following abbreviations will be used: Galactose-1-Phosphate, gal-1-P; Glucose-1-phosphate, G-1-P; adenosine triphosphate and diphosphate, ATP and ADP; uridinediphosphoglucose or —galactose UDPG and UDPgal.

in a conical graduated tube to separate the cells. After washing the cells with three changes of 10 ml. saline, the cell volume is noted.

The cells are lysed by shaking with two volumes of water and a little saponin, and by freezing. To the partially thawed haemolysate three cell volumes of ice-cold 20% trichloracetic acid are added: the mixture is shaken well and kept exactly six minutes in an ice bath, with occasional shaking; it is centrifuged for two minutes in ice-cold buckets and the supernatant is immediately poured through a sintered glass filter.

The filtrate, whose volume is measured, is transferred to a 15 cm. glass stoppered tube, containing three drops of 25% barium acetate, one drop of phenolphthalein solution and 5 ml. ethanol, previously cooled in ice. A slight excess of 40% KOH is added. It is important to carry out these operations quickly and to keep the mixture cold while the *p*H is acid, since the gal-1-P is easily hydrolysed in acid solution. The ice-cold mixture is acidified with the minimum amount of acid and then basified to a faint pink with 0·1N KOH. This solution is treated with four volumes of ethanol, re-neutralized if necessary, and kept in the refrigerator for at least two hours (or over night).

The precipitated barium phosphates are spun down and the supernatant is rejected.

Ice-cold neutralized 80% ethanol (10 ml.) is added and the precipitate is suspended by swirling the tube and then allowed to settle in the refrigerator for one hour. After centrifugation the supernatant is again rejected.

The residue is treated with 1·5 ml. 0·1N HCl and the mixture is immersed in boiling water and shaken to disperse the precipitate. The tube is stoppered (spring loaded) and immersed in boiling water for 15 minutes.

After cooling, the tube is centrifuged briefly and the hydrolysate is de-ionized as follows: it is transferred to a tube (10 × 1·5 cm.) containing 0·2 g. of Amberlite Monobed resin MB-1 (analytical grade), previously washed with several changes of boiled distilled water. The mixture is shaken mechanically for 15 minutes, keeping the resin as far as possible near the bottom of the tube. After a brief centrifugation the solution is transferred with a fine-tipped Pasteur pipette, reaching to the bottom of the tube, to a 5 ml. volumetric flask. The boiling tube is rinsed three times with 1 ml. of water, the separate rinsings being used to extract the resin for five minutes each time. The solution is transferred to the flask and the volume is finally made up to the mark.

Two aliquots of 2 ml. are transferred to evaporating cups, made by cutting off test tubes of 1·3 cm. diameter about 2·5 cm. from the bottom. The solutions are evaporated to dryness in a vacuum desiccator.

One of the cups is rinsed round with five or six portions of 50% methanol to dissolve the galactose and transfer it quantitatively to the starting line of a descending chromatogram. This is run on a sheet of no. 1 Whatman paper, 58 cm. long, with a 10 cm. long folded strip of paper stapled to the bottom. Known amounts of galactose (5–50 μg.) are placed alongside the sample. After 30 minutes' equilibration the chromatogram is run for 16 to 20 hours in ethyl acetate-pyridine-water (70 : 25 : 20 by vol.) at 27° C.

After drying at room temperature, the chromatogram is dipped in freshly prepared benzidine reagent (0·5 g. of decolorized benzidine in 5 ml. glacial acetic acid and 20 ml. acetone, to which 4 ml. 100% trichloracetic acid and acetone to 100 ml. is added) (Harris and MacWilliam, 1954). The chromatogram is heated for two to four minutes in an oven at 100° C. until the paper begins to turn pale yellow.

The amount of galactose in the aliquot used for chromatography is estimated visually by comparison with known amounts, either in daylight or in ultra-violet light, taking into account both the yellow colour (daylight) or greenish yellow fluorescence (u.v.) given by 0·2-10 μg. quantities of galactose, and the brown centres (non-fluorescent) given by larger amounts. The other aliquot of the de-ionized dried hydrolysate is available, if necessary, for making a closer assessment of the galactose content on the basis of the first result.

Results Obtained by the Improved Method. In four experiments in which pure gal-1-P had been added to a normal haemolysate and glucose-1-C^{14} to the hydrolysate, the recoveries were as shown in Table 1. It can be seen from this Table that about 90% of the labelled glucose has been recovered. The loss of about 10% of the glucose (probably due to irreversible adsorption on the resin) is, presumably, paralleled by a similar loss of galactose. A recovery of 90% is thus the best of which the method is capable. The maximum error involved in the visual assessment of galactose on the chromatogram is of the order of 10%. The over-all accuracy of this method can be considered adequate for the purpose of routine checks of erythrocyte gal-1-P levels.

TABLE 1

PERCENTAGE RECOVERY OF ADDED GAL-1-P FROM HAEMOLYSATE

Experiment	Glucose-1-C^{14}	Gal-1-P
1	93·1	100
2	90·2	92
3	91·2	84
4	88·8	100

Untreated Cases

Table 2 shows the gal-1-P levels found in untreated cases, aged 10-28 days, and in a patient of 4½ months after eight days on a milk diet. (The results reported below were obtained by the original method of Schwarz *et al.* (1956) as indicated in the introduction and are liable to be somewhat too low.)

With the exception of L.B. (whose clinical record was not available), the values are between 300 and 400 μg./ml., irrespective of age. This suggests that the galactose phosphate level may tend to a maximum attained after prolonged exposure of the cells to galactose.

TABLE 2
GAL-1-P IN UNTREATED CASES

Patient	Age	Gal-1-P (μg./ml. cells)
Susan B.	1½ weeks	360
S.B.	3 weeks	330
M.C.	4 weeks	300
L.B.	3 weeks(?)	130
A.J.	4½ months	400

Effect of Treatment

Fig. 1 shows the rate of progress of three infants. One of these (B.J.) was diagnosed at three days and was fed no milk from birth. Her cord blood contained 50 μg. gal-1-P/ml. cells, which must have been formed *in utero*.

After treatment for varying periods, the level of intracellular gal-1-P presumably depends on the galactose content of the diet. The scatter diagram (Fig. 2) shows the values obtained in 36 determinations on 13 patients and five normals. It can be seen that normal values are substantially less than the lowest found in treated galactosaemic infants.

Gal-1-P in Other Tissues

Organs from two infants who died from galactosaemia before the diagnosis could be made, were obtained at necropsy. In one case (M.C.) the material did not become available for analysis until several days after necropsy, having been left at room temperature in the meantime. The gal-1-P levels are, therefore, of no more than qualitative significance. The results are shown in Table 3, from which it is clear that gal-1-P might reasonably be expected to accumulate in all tissues of the body.

A biopsy specimen of liver taken at laparotomy from a patient in whom haemolytic disease of the newborn as well as other complicating factors were present in addition to galactosaemia, contained 50 μg. gal-1-P/g. after four months of treatment. The galactose phosphate level in the erythrocytes was estimated at the same time and found to be 64 μg./ml.

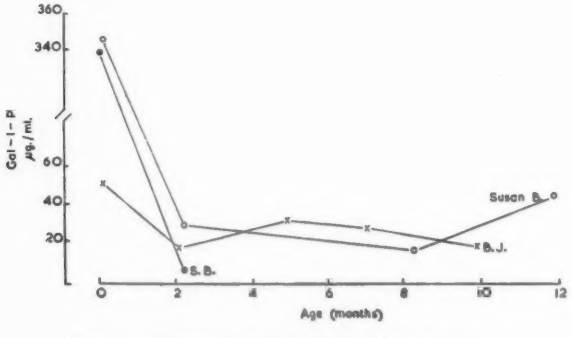

FIG. 1.—Change in gal-1-P levels during treatment.

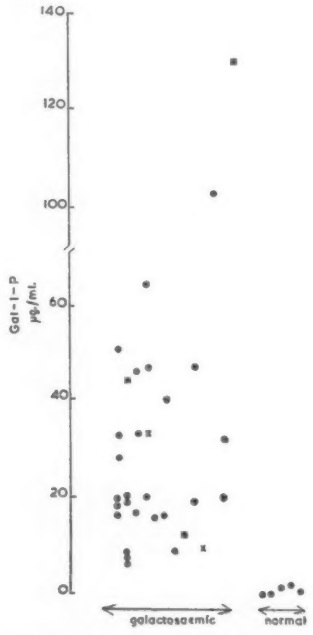

FIG. 2.—Erythrocyte gal-1-P in treated patients. × indicates blood analysed shortly after exchange transfusion, hence low gal-1-P levels do not reflect adequate treatment.

TABLE 3
GAL-1-P IN ORGANS

Organ	Patient M.C. (μg./g.)	Patient L.C. (μg./g.)
Whole blood	—	270
Liver	20	90, 75*
Kidney	3	145
Brain	0	65, 69*
Tongue	—	87
Adrenal	4	—
Heart	20	—
Gallstones	22	—

Discussion

There is now considerable evidence that gal-1-P, by interfering with the normal metabolism of the cell, may be responsible for the clinical manifestations of galactosaemia. The demonstration that the phosphate accumulates in a variety of tissues of the galactosaemic infant if his diet contains galactose, is in line with the diversity of the symptoms. Even if all tissues are liable to suffer damage from the accumulation of the 'toxic' phosphate, in some the existence of sufficient functional reserve would prevent this damage from manifesting itself clinically.

It may be mentioned here that Schwarz and Golberg (1955) showed that the lens capsules and epithelia of rats suffering from galactose cataract

contained approximately 170 μg. gal-1-P/g., whereas non-cataractous lenses of galactose-fed animals contained not more than 0·1 of this amount. Recently, Lerman (1960) has shown that an inhibition of lenticular G-6-P dehydrogenase and of glucose catabolism is demonstrable two to four days after instituting a high galactose diet, and that the ATP content of the tissues drops to very low levels. This interference with normal metabolism might well result from the accumulation of gal-1-P and probably accounts for the gradual opacification.

If one accepts the premise of the 'toxic' nature of galactose phosphate, the question arises at what concentration this substance begins to exert its deleterious effect on cellular metabolism. Unfortunately, it is not yet possible to offer an answer, since it is difficult to simulate intracellular conditions *in vitro*. In erythrocytes a gal-1-P concentration of 150 μg./ml. was found to inhibit cellular respiration by 30% (Schwarz *et al.*, 1956), but other, metabolically more active, cells might be more or less affected by such levels. It was pointed out, in connexion with Table 2, that in untreated cases the galactose phosphate concentration rises to what appears to be a maximum of 300-400 μg./ml. Since this level would be reached quite rapidly (12-16 hours, in the presence of sufficient galactose to saturate the enzyme) (Kalckar *et al.*, 1956), it seems that the accumulation of the phosphate is self-limiting, i.e. analogous to the well-known product inhibition of hexokinase.

Since it is not known what constitutes a 'safe' level of intracellular galactose phosphate and since both its rate of formation and its rate of removal may be different in each tissue, the determination of galactose phosphate in erythrocytes can probably furnish no more than an indication of whether the general tissue level is rising or falling. On the single occasion when a biopsy specimen of liver could be examined, the galactose phosphate level was close to that in the erythrocytes, but in the necropsy specimens the levels differed considerably.

The presence of a fairly substantial amount of gal-1-P in the cord blood of a galactosaemic infant raises the question of the mother's diet during pregnancy. In the case recorded no galactose could be detected chromatographically (i.e. less than 5 mg. %) in the mother's venous blood on two occasions after the consumption of one pint of milk. From this one may infer that the galactose phosphate had accumulated in the foetal tissues by prolonged exposure to small amounts of galactose transferred across the placenta.

From the results presented in this paper and from clinical findings reported previously (Komrower *et al.*, 1956), it is clear that, ideally, the galactosaemic infant should be provided with a completely galactose-free diet. In practice such treatment is fraught with difficulties due both to the wide distribution of galactose and to the degree of conscientiousness required on the part of the mother. It should be emphasized here that many foods contain galactose in the form of α-galactosides (lactose is a β-galactoside) which may not be hydrolysed to free galactose in the intestinal tract. But until it is known for certain that no galactose is liberated either by the digestive enzymes or by the intestinal flora, foods containing α-galactosides should be avoided (Schwarz, Holzel, Stapleton and Goodell, 1959).

In view of the practical difficulties associated with the diet, regular assessment of the gal-1-P level in the erythrocytes constitutes a ready, and indeed the only, means of checking the adequacy of the diet, from the point of view of exclusion of galactose. The disappearance of frank symptoms is probably not a reliable indication that treatment is adequate and successful, especially as the developing nervous system may be more sensitive than other tissues to a slight but persistent interference with normal metabolism.

Final judgment on the effect of ingesting small amounts of galactose and consequent accumulation of the phosphate in the tissues has to be deferred until more information is available on the maximum level which can build up in the cell without interfering with metabolism. It is, however, well to consider that a uniform distribution of gal-1-P in the total intracellular water corresponding to a level of 150 μg./ml. erythrocytes, which is known to affect erythrocyte metabolism, would be equivalent to about 400 mg. of galactose for a 7 kg. infant. Since a much lower concentration of the phosphate might turn out to be damaging, it will be appreciated that the amount of galactose involved is quite small. Thus, a 'low lactose' milk, claimed by the manufacturers to contain, in the reconstituted condition, not more than 0·012% galactose, i.e. equivalent to 400 mg. in 3½ litres., would supply what might be a highly toxic dose in a few days.

It should, however, be emphasized that apart from the gaps in our knowledge of the degree of toxicity of gal-1-P and of the rate of accumulation in different tissues, there is bound to be a considerable variation from one individual to another, due to the variability of such factors as rate of absorption, renal efficiency and, above all, a residual capacity to metabolize galactose by the usual or an alternative pathway (Isselbacher, 1957). In consequence it is impossible to dogmatize on the

precise significance of particular galactose phosphate levels. Until the gaps in our understanding are closed, a cautious approach is indicated.

Summary

Hereditary galactosaemia is characterized by a deficiency of the enzyme galactose phosphate uridyltransferase, which catalyses the conversion of galactose-1-phosphate to glucose-1-phosphate. The deficiency leads to an intracellular accumulation of gal-1-P when the patient's diet contains galactose. There is evidence indicating that this phosphate inhibits a number of enzymes and that by these, or other, means it interferes with normal cellular metabolism.

Analysis of necropsy material has shown that galactose phosphate is deposited in several, if not all, tissues, thus probably accounting for the diverse ill-effects constituting the galactosaemic syndrome. The determination of gal-1-P in the erythrocytes affords a ready means of assessing the adequacy of treatment, of which the disappearance of frank symptoms is an insufficient guide. The amounts of galactose potentially capable of damaging cellular metabolism are quite small. This fact and the wide distribution of galactose impose a heavy burden on the galactosaemic patient's mother and clinician alike, thus rendering a regular check by galactose phosphate determination desirable.

An improved method for the estimation of galactose phosphate in erythrocytes is presented.

I would like to thank the many paediatricians who have referred their patients to me and have given their permission to incorporate the results in the scatter diagram. I wish to express my appreciation for the supply of necropsy material by Dr. L. L. R. White and Dr. J. L. Emery. I am indebted to Professor W. Gaisford and Dr. A. H. Gowenlock for valuable discussion. The analyses and much of the development work were carried out by Miss Naomi Simpson, whose skill and patience it is a pleasure to record.

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TREATMENT OF ENCEPHALOTRIGEMINAL ANGIOMATOSIS (STURGE-WEBER DISEASE) BY HEMISPHERECTOMY

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Encephalotrigeminal angiomatosis or Sturge-Weber's disease is an uncommon congenital disorder which can vary greatly in the extent of its manifestations, but which in severe cases can lead to infantile hemiplegia associated with fits, behavioural disorders and mental backwardness. Until comparatively recently specific therapy was largely limited to anticonvulsant drugs. Only a few isolated reports of surgical intervention have been recorded. The purpose of this paper therefore is to describe the findings and results of surgery in five consecutive patients with infantile hemiplegia treated by hemispherectomy and since followed up for from three to eight years who improved as regards epilepsy and personality disorders, although not as regards hemiplegia. A preliminary report on the first two of these cases has already been presented (Polani, 1952).

Excellent reviews of the clinical manifestations and pathogenesis of the condition have recently been given by several authors (Medoc, Sotelo, Arana Iñiquez and Estable Puig, 1953-1954; Lichtenstein, 1954; Wohlwill and Yakovlev, 1957; Norman, 1958; Peterman, Hayles, Dockerty and Love, 1958). The essential lesion appears to be a venous angiomatosis of the leptomeninges generally over one cerebral hemisphere, most often in the posterior parietal and occipital regions, associated with a port-wine naevus of the skin of the face in the territory of one or more divisions of the trigeminal nerve, on the same side of the body. Occasionally both cerebral hemispheres are involved, and the cutaneous naevus may also be in other parts of the body. In all cases the affected areas of cortex become atrophic with the deposition of calcium and ferruginous materials that give rise to a characteristic curvilinear appearance on radiographs. Other lesions that may be present include angioma of the choroid of the eye and ipsilateral buphthalmos or glaucoma. Dural and diploic vascularity is exceptional.

The first recorded case description is that of Rudolf Schirmer (1860) who described a 36-year-old patient with an extensive naevus involving both sides of the face, left more than right, as well as the chest and abdomen. He did not mention any neurological features, but pointed out that the patient's left eye protruded, and that there was hydrophthalmos and varicosities of the retinal veins. Allan Sturge (1879) demonstrated to the Clinical Society of London a girl of 6½ years of age who had an extensive 'port-wine mark' over the right side of the head and face with enlargement of the right eye and vascular changes in the choroid. He inferred that her left-sided fits were caused by a similar vascular lesion of the right side of the brain. Kalischer (1897) gave the first autopsy report of this condition. He (1897; 1901) described an extensive telangiectasis of the scalp and the surface of the brain, all on the same side. He did not, however, observe any calcification, presumably because his subject was only 1½ years old. Hebold (1913) was the first to note the cerebral calcification, but did not determine its precise situation. However, Weber (1922; 1929) was the first to publish a radiograph of the double curvilinear shadows that outline the sulcal pattern, although according to Krabbe (1934) Wissing, in 1921, had demonstrated these features to the Radiological Society of Copenhagen. It was Krabbe (1934) himself who demonstrated that the calcium deposits occurred within the cortex and not in the angiomatous vessels. Dimitri (1923), from the Argentine, also published an early description of the radiological appearances.

By this time the essential features of the disease were all recorded, but there has been some difference of opinion over nomenclature. 'Sturge-Weber disease' or 'Sturge-Weber syndrome' have become sanctioned by usage, although Weber (1936) disclaimed the use of his name and suggested that it be called 'Sturge-Kalischer disease'. It has also been called 'Krabbe's disease', and 'Sturge-Weber-Dimitri disease' (Lichtenstein, 1954), and 'Sturge-Weber-Krabbe's disease' (Krayenbühl, Yaşargil and

Uehlinger, 1957). Of the non-eponymous terms 'encephalotrigeminal angiomatosis' or 'meningo-facial angiomatosis' seem the most accurate. In making the diagnosis it must be remembered that, like most congenital malformations, the syndrome may be incomplete. It is therefore advisable to limit the definition of Sturge-Weber disease to cases showing at least two of the major signs, such as facial naevus combined with either intracranial angioma or with angioma of the choroid of the eye (Poser and Taveras, 1957; Norman, 1958). This rules out many superficially allied conditions such as spinal cord angiomas with cutaneous naevi of metameric distribution, cutaneous naevi with cerebellar symptoms, and the familial non-calcifying meningeal angiomas (Norman, 1958), and also the cerebral calcification epilepsy of Geyelin and Penfield (1929).

Technique of Hemispherectomy in Sturge-Weber Disease

As all the cases in our series were operated upon in the same way, it will be convenient to outline the surgical technique used before proceeding to the case reports. To Krynauw (1950) must be given the credit for introducing, on a sound and systematic basis, the operation of hemispherectomy as a method of treating epilepsy and behavioural disorders in patients with infantile hemiplegia from various causes. The technique advocated by him, which has been followed by others (Cairns and Davidson, 1951; Gros, 1951; McKissock, 1953 and 1954), was to remove the cerebral hemisphere in segments. Obrador Alcalde (1950 and 1952), however, removed the affected cerebral hemisphere in one piece, and a similar technique was employed in all our cases. This technique stems from the original work of Dandy (1928), who first removed the cerebral hemisphere of a patient because of a glioma, and has since been adopted by others (Gros and Vlahovitch, 1954; French, Johnson, Brown and Van Bergen, 1955).

All our operations were performed under general anaesthesia without the use of hypothermia or of arterial hypotension. A large fronto-temporo-parietal craniotomy is turned extending medially from the midline to the floors of the anterior and middle cranial fossae laterally. The scalp incision is outlined in Fig. 5. Beneath it the bone flap is cut and pedicled on the temporal muscle. The dura is then opened in such a way that it can be sutured later. After the preliminary inspection of the hemisphere the first step in the excision is to elevate the frontal lobe and open up the inner part of the sylvian fissure so that the middle cerebral artery can be clipped and then divided just distal to its central perforating branches. This step lessens subsequent bleeding.

Attention is then turned to the region of the sagittal sinus, and the veins entering it from the superior margin of the hemisphere are coagulated and divided from before laterally. This enables the hemisphere to be retracted from the falx, exposing the mesial surface of the opposite cerebral hemisphere, the corpus callosum and the two anterior cerebral arteries. The ipsilateral anterior cerebral artery can then be divided a little distal to the anterior communicating artery, while the ipsilateral edge of the corpus callosum is then incised from its genu anteriorly to its splenium posteriorly so exposing the interior of the lateral ventricles. Retraction of the hemisphere permits the caudate nucleus to be identified, and separation of the hemisphere from the basal ganglia and thalamus is commenced by dividing the cerebral substance along the lateral edge of the nucleus towards its tail. This cut is extended until the temporal horn is laid open. The surgeon then returns to the genu and after dividing the rostrum of the corpus callosum, he divides the frontal cortex immediately in front of the chiasm and optic nerve, so opening into the cut through which the middle cerebral artery was severed. This is then extended subpially along the infero-medial temporal border removing the uncus and hippocampus, the free edge of the tentorium being followed, and the posterior cerebral artery being severed. The penultimate stage is now reached whereby the cortex and white matter of the isthmus of the limbic lobe is divided right through from the trigone of the lateral ventricle to the tentorial opening. The last stage of removal is undertaken by dividing the veins which pass from the occipital pole to the various venous sinuses. Finally, the choroid plexus is coagulated to prevent excessive cerebrospinal fluid formation, as so much of the absorbing area has been taken away with the resected hemisphere. The dura is then closed and the cavity filled with Ringer's solution. The bone and scalp flaps are replaced.

A blood transfusion is given during the operation. Recovery is usually rapid. The only complication encountered in this series was an indolent infection in Case 1 of the large dead-space between the sutured dura and the skull. This was controlled by antibiotics and eventually cured by removing a small sequestrum that had formed at the centre of the inner table of the skull. In two hemispherectomies for infantile hemiplegia for other lesions, one of us (M.A.F.) has also encountered the complication of a communicating hydrocephalus involving the operative cavity with the ventricular system and spinal subarachnoid space. It appears to be due to the brain-stem shift described by Cabieses, Jerí and Landa (1957), and in both cases was relieved by reopening the craniotomy and dividing the tentorium cerebelli so relieving the upward thrust of the midbrain and cerebellum. This complication occurred even though the choroid plexus had been coagulated.

Removal of the cerebral hemisphere in the manner described is no more difficult than the technique employed by Krynauw, and has the advantage of procuring a specimen that is intact.

Case Reports

Case 1. R.D., 3½ years of age, was referred by Dr. P. R. Evans. This boy was born with a left facial naevus. Seizures started at the age of 4 months, and were characterized by clonic movements of the right

mbs, and deviation of the head and eyes to the right. At first they occurred in clusters every day for a week, followed by periods of freedom of up to four months, but later, in spite of intensive medication with phenobarbitone, potassium bromide and phenytoin, they occurred several times daily. Weakness of the right arm and an extensor plantar response were first noted when he was 13 months old, but radiographs of his skull at that time were reported to be normal, although encephalography showed a shrunken left hemisphere. An arteriogram was also said to be normal. There were no temper tantrums, but he was sullen, moody and irritable.

EXAMINATION. He was small, pallid and underdeveloped; he was very backward, and could only utter a few words; he understood simple commands and could point out objects. The naevus was patchy and involved the ophthalmic and maxillary divisions of the territory of the left trigeminal nerve (Fig. 1). No bruit

FIG. 1.—Case 1, before operation, showing characteristic naevus which has been partially bleached by past applications of carbon dioxide snow.

was heard over the skull. The optic fundi were normal. A right homonymous hemianopia was demonstrable by menace. There was a right-sided infantile hemiplegia characterized by some wasting and shortening of the limbs with spastic weakness; this weakness was slight in the lower face. Motor power at the shoulder and elbow was reduced about 50%. He could grip feebly with his fingers, but could not extend his right wrist or fingers. The weakness was less obvious in his right leg where he could dorsiflex his ankles and move his toes. The tendon jerks were increased in right arm and leg and the right plantar response was extensor. He responded equally to pinprick on both sides of the body. He walked only with great difficulty. The left limbs were normal.

INVESTIGATIONS. Skull radiographs showed gross reduction in size of the left half of the cranial cavity, while the sulcal pattern of practically the whole of the left cerebral hemisphere (except for the frontal region) was outlined by the characteristic double-paralleled, sinuous, curvilinear lines (Figs. 2 and 3). Pneumoencephalography showed that the ventricular system

FIG. 2.—Case 1, straight lateral radiograph of skull, showing characteristic calcification.

FIG. 3.—Case 1, antero-posterior air encephalogram, showing smallness of left cerebral hemisphere.

was of normal size and shape, although displaced to the left because of the atrophy of its left cerebral hemisphere. Electroencephalography disclosed greatly diminished activity over the left cerebral hemisphere without definite spiking or other epileptic activity.

OPERATION. A large left-sided craniotomy was performed on August 15, 1951, under general anaesthesia. The whole convexity as seen through the craniotomy appeared red and congested with a fine network of small blood vessels closely meshed. These tiny blood vessels were in the subarachnoid space and they, together with cerebrospinal fluid, had elevated the arachnoid off the cortex so that at first the sulcal pattern could not be discerned (Fig. 4). When, however, the arachnoid

FIG. 4.—Case 1, operative appearances of left cerebral hemisphere as seen from the head of the operating table. Notice that whereas the pia-arachnoid alongside the superior longitudinal sinus is still lifted off the cortex, the convolutional pattern over the convexity of the cortex is becoming apparent as cerebrospinal fluid drains away from the sulci.

was pressed upon firmly with a glass slide, the subarachnoid spaces emptied so that one could see pale cortex between the interstices of the vascular network. The network itself did not blanch. Later this network was found to involve the whole surface of the left cerebral hemisphere on its medial and inferior aspects as well as over the convexity. The whole left hemisphere except for its thalamus and caudate nucleus was then removed in one piece. The patient stood the operation well. His immediate recovery from operation was excellent (Fig. 5), but six weeks later a low intermittent pyrexia commenced. An abscess appeared under the scalp and was controlled by aspiration and antibiotics. There remained a residual discharging sinus in the temporal fossa which did not finally heal until a small sequestrum was removed from the inner table at the centre of the bone flap one year after the original operation.

PATHOLOGY. Photographs of the specimen after operation gave a poor impression of the vascularity of the subarachnoid network (Fig. 6), but a radiograph showed the characteristic double curvilinear lines with great clarity (Fig. 7). The specimen was preserved in the Gordon Museum, Guy's Hospital, after two blocks had been taken for histological examination. Dr. A. L. Woolf subsequently reported on these blocks as follows:

> 'The pia arachnoid was extremely vascular, the vessels resembling arterioles and venules, but in both cases having an unusually thick collagenous coat (Fig. 8). This coat was rich in fibroblasts. The arterioles had a well-marked muscular media. Occasionally this muscular coat was very thick indeed. Deep to the pia was a thick feltwork of glial fibres. In the cortex itself loss of nerve cells was confined to perivascular clearings, but there was much gliosis. There was no increase in microglia. There were very numerous calcospherites throughout the cortex and white matter of the occipital lobe, but an origin in calcified blood vessels could not be definitely shown. The capillaries in the cortex were increased in prominence and some had unduly thickened walls. Calcospherites were less numerous in the frontal lobe.'

PROGRESS. He has since been followed for over eight years, and has been completely free of fits and no anticonvulsant medication has been administered during that time. For the past three years he has been attending a school for physically handicapped children. He plays well with other children, and is not unduly aggressive or timid. Mentally, he is backward, but he is educable and interested in what goes on. He can read and write simple words and perform simple arithmetic, but his mental age is probably 7 years (Schonell R.; age 6 years 10 months, when actually 11 years old—D. Shalman). He has a right homonymous hemianopia. The right arm is held with the wrist flexed. He has good movements at the shoulder and a useful grip in the right hand which he uses to steady objects. The right leg is 2 cm. shorter than the left, and although the leg is generally weak, he can walk with surprisingly little limp. The degree of hemiparesis has not been altered by operation. He was reported by his school teacher to be 'sociable and affectionate'.

Case 2. A.McK., 6 years of age, was referred by Dr. P. R. Evans. This girl was born with a port-wine stain of the left side of her face and scalp. She appeared otherwise normal until the age of 3 months when she began to have seizures involving the right side of her body. At first these were severe and frequent, lasting up to 10 minutes, and not responding noticeably to phenobarbitone. Generalized convulsions occurred at times. In her first two years of life she also had six separate attacks of pneumonia. Investigation elsewhere by left carotid arteriography was said to be normal,

FIG. 5.—Case 1, appearances of wound 15 days after operation.

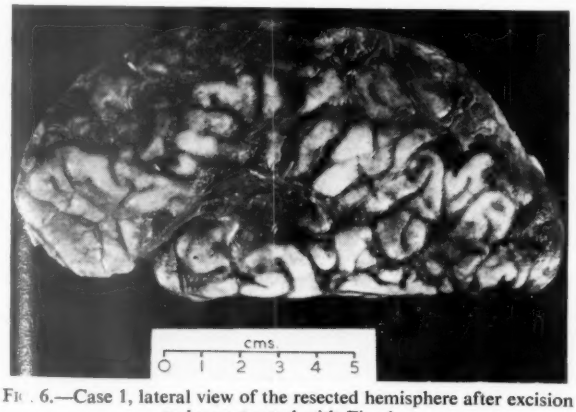

FIG. 6.—Case 1, lateral view of the resected hemisphere after excision to be contrasted with Fig. 4.

FIG. 7.—Case 1, radiograph of resected specimen after removal of two blocks for histological examination.

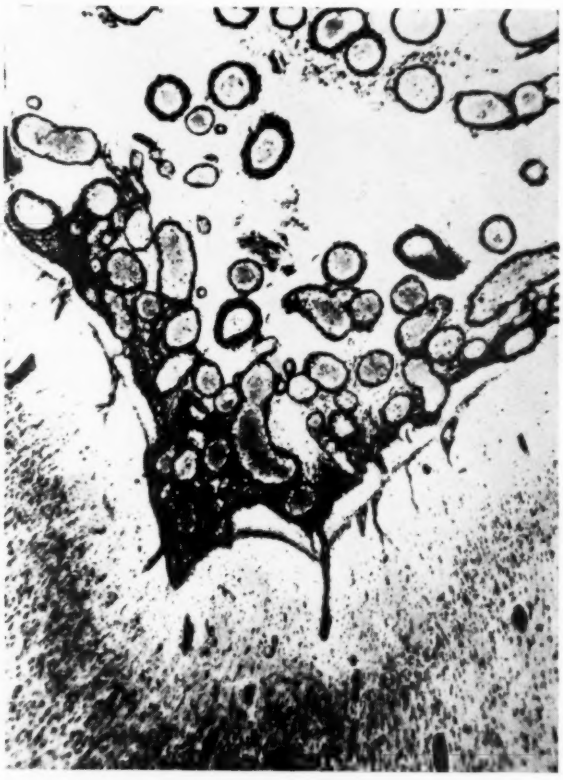

FIG. 8.—Case 1, photomicrograph showing numerous abnormal arterioles and venules in leptomeninges and also in outer layers of cortex. Cresyl violet × 41.

while pneumoencephalography showed gross atrophy of the left cerebral hemisphere. There was no mention of cerebral calcification. By the age of 18 months it was evident that her right limbs were weak and spastic, and by the age of 6 years her fits had become milder and would often only involve the right limbs without loss of consciousness. However, she would then average two to three attacks per week in spite of sedation with various anticonvulsant drugs. She did not talk until she was 2 years old, nor walk until she was 4 years. At 6 years she could say only a few simple words, and recognize and sing simple nursery tunes. Her behaviour had recently begun to deteriorate. She would fly into tempers if thwarted or disappointed, and in these tantrums she would scream, stamp and throw things around for periods of up to half an hour.

FIG. 9.—Case 2, photographed 15 days after operation to show extent of naevus as well as the scalp incision.

EXAMINATION. She was thin and undersized. The telangiectasis involved the left side of her face in the distribution of the upper two divisions of the trigeminal nerve (Fig. 9). She spoke in simple words and was not dysphasic. Her mental age was between 2 and 3 years (E. Norman). Her optic fundi were normal, but she showed a right homonymous hemianopia. There was an inconstant divergent strabismus. The right lower face was weak. The right arm was somewhat wasted and spastic, and about 3 cm. shorter than the left. It was held flexed at the elbow, forearm hyperpronated, and with wrist and fingers flexed. Proximal movements were better preserved than distal, and she could abduct the shoulder against gravity, but her hand grip was feeble. The right leg was 4 cm. shorter than the left with a spastic talipes equino-varus deformity. Muscle power was greatly diminished in all groups, but she could walk and even run unassisted although with a limp. She reacted equally to pinprick on both sides of the body.

INVESTIGATIONS. These were similar to those of Case 1. Radiographs of the skull showed that the left half of the cranial cavity was smaller than the right with extensive sinuous calcification of the left hemisphere (Fig. 10). On pneumoencephalography no air entered the ventricular system, but there was an extensive accumulation of subarachnoid air on the left side. Electroencephalography under seconal sedation showed absence of activity over the whole of the left hemisphere. No epileptic discharges were seen.

OPERATION. This was performed on April 1, 1952. The procedure and the appearances were similar to those observed in Case 1. Immediately on recovery from the anaesthetic, the condition of the right limbs was found to be unchanged. Her postoperative recovery was straightforward.

PATHOLOGY. The macroscopic and radiographic

FIG. 10.—Case 2, straight radiographs showing characteristic calcification together with atrophy of left cerebral hemisphere.

appearances of the specimen were similar to Case 1. Dr. Barbara Smith reported as follows:

'The pia-arachnoid was thickened and contained a collection of abnormal vessels (Fig. 11). In the

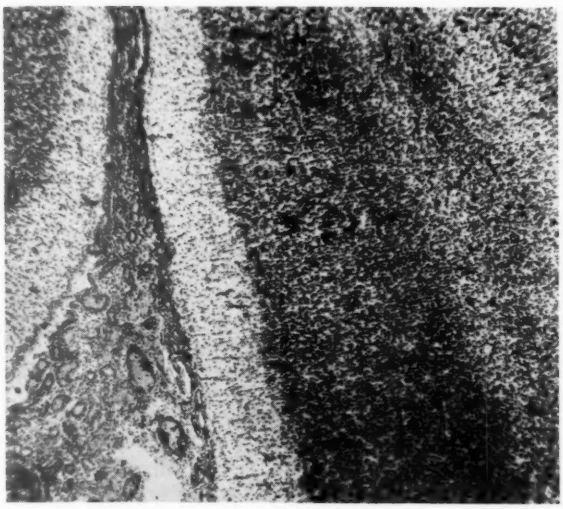

FIG. 11.—Case 2, photomicrograph showing thickened and abnormally vascular leptomeninges overlying an area of cortex which is gliotic and contains scattered calcospherites. Cresyl violet × 26.

occipital block there was very marked subpial gliosis. This was less apparent in the frontal region. There were an increased number of astrocytes in the grey and white matter. Some of the pyramidal cells especially in the third layer appeared shrunken. Calcospherites were scattered throughout the cortex and white matter.'

PROGRESS. She has since been observed for seven and a half years, and during that time has been completely free of seizures. Although rather excitable, she is good at home and has no behaviour disorder. She remains, however, very backward although educable. Her mental age at 7 years 4 months on the Merrill-Palmer scale was 3 years 11 months, i.e. I.Q. 53 (E. Norman). At 13 years her mental ability as judged by reading primers, was 7 to 8 years. She attends a special school, and has participated in television performances. The hemiparesis and hemianopia are unchanged. She can appreciate light touch and pinprick equally on both sides, but two-point discrimination and postural sensibility is grossly impaired on the right side.

Case 3. S.W., 3½ years of age, was referred by Dr. P. R. Evans. This girl was born with a naevus of the right forehead. Starting at the age of 3 weeks, she had a series of fits in which she would become rigid and cyanosed for a few seconds. These fits kept recurring two to six times daily for a period of three weeks, and have not since recurred. When she was 12 months old it was first noticed that she was liable to burst into screaming attacks. These attacks occurred whenever she craved attention, and once she received this she quietened down. In the tantrums she would frequently bang her head on the floor. At the age of 18 months her left limbs were first noticed to be weak, and subsequently the weakness gradually became more pronounced. She sat up at the age of 15 months, and walked at 2 years. Hemispherectomy was first considered when she was 18 months old, but as she was free of fits, it was decided to wait. However, her personality disorder and temper tantrums became so marked that she was almost unmanageable. She was, therefore, admitted at the age of 3½ years for operation.

EXAMINATION. She was a thin, irritable girl, who could, however, be pleasant when she was allowed to have her own way. There was a naevus of the right forehead in the distribution of the ophthalmic division of the trigeminal nerve (Fig. 12). The optic fundi were normal, but there was a left homonymous hemianopia. There was also a left infantile hemiplegia of marked degree. The left limbs were a little shorter and smaller than the right. The left arm was held across the chest with the fist clenched and the elbow flexed to a right

FIG. 12.—Case 3 before operation in a temper tantrum.

angle. She walked with a spastic left foot drop. Psychological testing showed that her mental age on the Merrill-Palmer scale was 2 years and her intelligence quotient was 56 (Stanford Binet Form L.—Miss M. Newell).

INVESTIGATIONS. Skull radiographs showed the right half of the cranial cavity to be smaller than the left

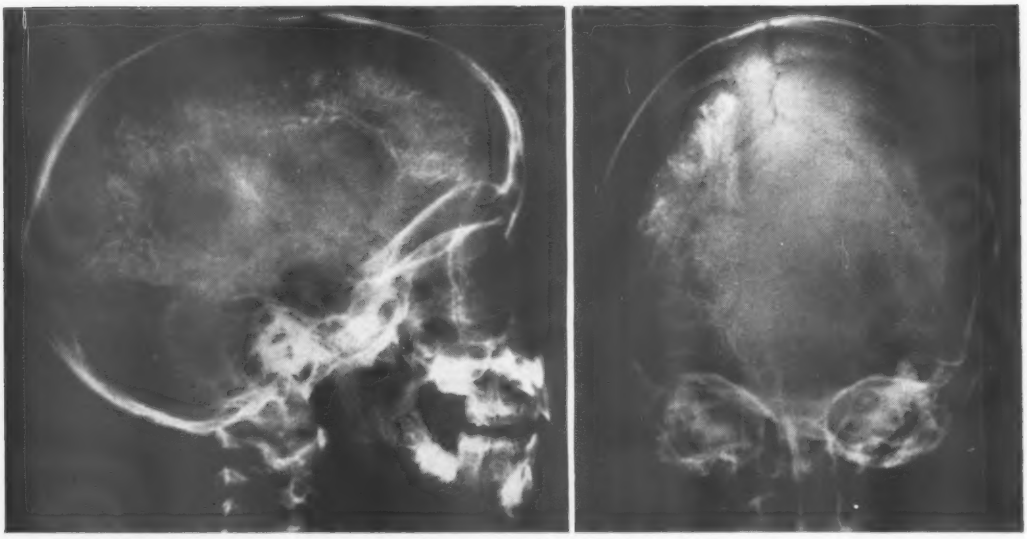

FIG. 13.—Case 3, radiographs showing characteristic calcification and right cerebral atrophy.

with extensive calcification in the right cerebral hemisphere of characteristic Sturge-Weber type (Fig. 13). A seconal E.E.G. record showed almost total absence of rhythmic activity over the right hemisphere with normal sleep rhythms on the left. There was no epileptic activity.

FIG. 14.—Case 3, 17 months after operation.

OPERATION. A right lateral craniotomy was performed on March 30, 1954, with similar findings to the preceding cases. The whole right cerebral hemisphere presented a typical telangiectatic blush with a fine network of venous angiomatous vessels in the leptomeninges. The right hemisphere was removed in one piece except for its basal ganglia. The postoperative recovery was smooth.

PATHOLOGY. The macroscopic and radiographic appearances of the specimen were similar to those of the preceding two cases, but unfortunately the specimen was subsequently mislaid and no pathological studies were made.

PROGRESS. Since then her progress has been reasonably good, although she has functioned at a defective level. She has had no fits and no temper tantrums and her parents describe her behaviour as satisfactory. At the age of 5 years (Fig. 14) the Stanford-Binet Form L. gave her mental age as $3\frac{1}{2}$ years and her I.Q. as 63. Since then she has made reasonable progress at school, and now, at the age of $8\frac{1}{2}$ years, can just read and write. Her left upper limb has remained very weak and is held flexed across her chest as before without any useful grip in the left hand. The left leg showed very little weakness, and the gait was only slightly abnormal. A number of tenotomy operations have been performed to correct a talipes equinus. Her present full scale intelligence quotient on the W.I.S.C. scale is 75 (D. Shalman), and she is attending a school for educationally subnormal children (Dr. A. C. Blandy).

Case 4. G.L., 16 years of age, was referred by Dr. N. Acheson. This youth, the eldest patient in our series, was born with a naevus covering most of the left face,

patchily over much of his body on the left side and to a slighter extent on the right side. A right hemiparesis was noted in early infancy. From the age of 4 months onwards he exhibited frequent epileptic attacks in which he rubbed his hands together, had slight twitches of his limbs, and was out of contact for one to two minutes. From the age of 14 years he had major convulsions lasting three to five minutes and recurring every four to six weeks in spite of medication. He had always been mentally defective and aggressive, and in recent years had exhibited frequent temper tantrums. His parents assessed his mental age as 4 to 5 years, and treated him as such. He wet his bed most nights.

EXAMINATION. He was small (5 ft. 2 in.) and underdeveloped. The naevus was extensive not only over the left face (Fig. 15), but over much of his body as well (Fig. 16). The left retina was a deeper red than the right and the left eyeball was bigger than the right. However, he appeared to see equally well with each eye, although a right homonymous hemianopia was present. A typical right-sided infantile hemiplegia was present with shortened spastic right limbs. His speech was limited to simple sentences, but he could neither count beyond 10 nor tell the time on a watch. He named common objects correctly. He stood in a stooped position and limped when he walked. His secondary sexual development seemed normal. An attempt was made to assess his intelligence quotient, but he proved untestable (Dr. V. Meyer).

FIG. 15.—Case 4, showing left facial naevus and left buphthalmos.

FIG. 16.—Case 4, showing patchy naevus over trunk.

INVESTIGATIONS. Skull radiographs showed a clear hemicranial atrophy with several large irregular blobs of calcification scattered throughout the left cerebral hemisphere (Fig. 17). Only in the occipital region could the double curvilinear lines which are more characteristic of Sturge-Weber disease be discerned. Pneumoencephalography disclosed a normal-sized ventricular system with, as in Case 1, considerable pooling of air in the subarachnoid spaces over the left cerebral cortex. The electroencephalogram showed almost complete absence of activity over the left hemisphere with normal alpha activity on the right side. No epileptic activity was seen in the routine records, but in a special study employing sphenoidal electrodes and thiopentone narcosis (Pampiglione and Kerridge, 1955) an active focus of spike discharges, both surface-negative and surface-positive was seen at the right sphenoidal area. We presumed, on clinical grounds, that this focus was being paced from the left side.

OPERATION. A left-sided craniotomy, performed on March 9, 1956, revealed an extensive angiomatous malformation of the Sylvian veins extending 6 cm. by 3 cm. (Fig. 18). The subarachnoid spaces over the rest of the hemisphere were covered with a close network of finer veins. Electrocorticography revealed a surprising amount of irregular slow-wave activity in the diseased hemisphere. The entire hemisphere except for its basal ganglia was then removed in one piece without much difficulty.

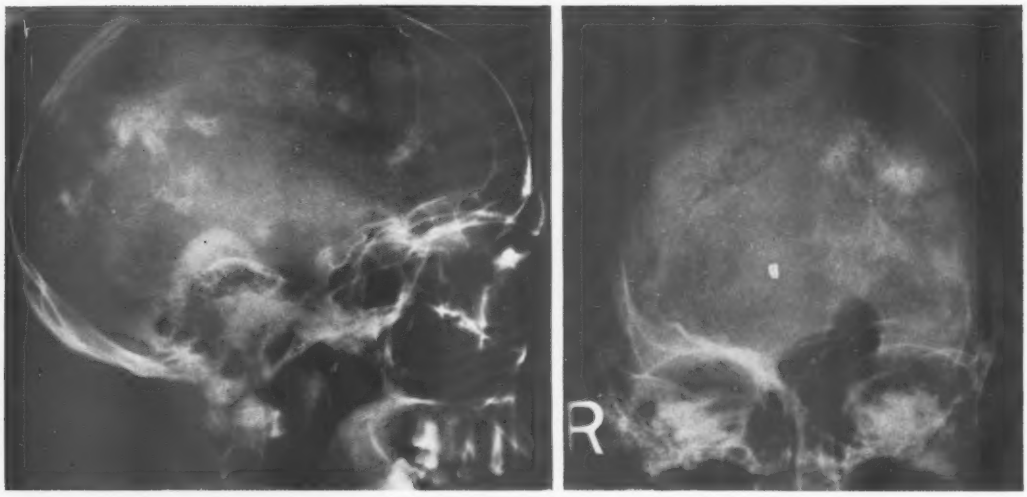

FIG. 17.—Case 4, radiographs showing peculiar type of cerebral calcification.

PATHOLOGY. Dr. Barbara Smith reported that two blocks of cortex showed 'a mass of dilated abnormal vessels embedded in connective tissue. In the outer layers of the cortex and in the white matter there were large masses of calcium, particularly in relation to the depths of the sulci. There was some gliosis of the cortex'. A diffuse angioma was present in the subarachnoid space (Fig. 19). A portion of the scalp with the naevus showed that the 'dermal papillae were more vascular than normal'. In the choroid plexus 'there was only a small area of normal choroid plexus. The rest consisted of an angioma with a number of calcified nodules'. A piece of the cranial vault showed 'no abnormality'.

PROGRESS. He made a good recovery from operation but there was no change in his neurological signs. His behaviour, however, was very much improved, and a month after operation it proved possible to assess his intelligence on the Wechsler-Bellvue scale (I.Q. 30). Three years later his parents reported that he had had no fits since operation, and was 'more even-tempered and manageable'.

FIG. 18.—Case 4, operative appearances of left cerebral hemisphere as viewed from the head end of the operating table.

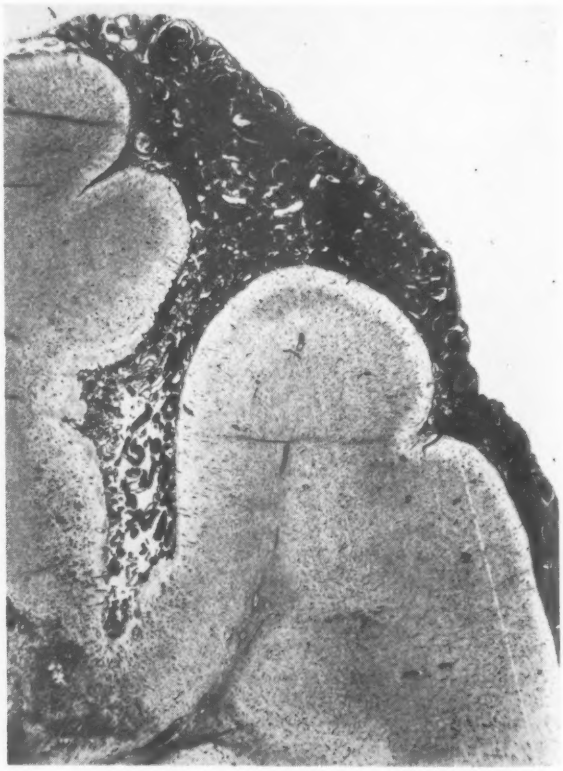

FIG. 19.—Case 4, photomicrograph showing a diffuse leptomeningeal angioma, extending into a sulcus. The cortex in the floor of the latter shows scattered masses of calcium. Haematoxylin and van Gieson × 7.

Case 5. R.W., 12 years of age, was referred by Dr. I. MacKenzie. This boy was born with a naevus in the left forehead. At the age of 4½ months his mother noticed that he appeared disinclined to use the right hand. His progress between the ages of 4½ months and 2 years was slower than normal, and he did not walk until he was 2 years of age. At the age of 9 months he began to have convulsive seizures involving the right side of the body with loss of consciousness. These continued ranging in frequency from as many as 20 a day to as few as two or three a week. He started at an ordinary school when 5 years old, but at the age of 7 years was sent to a special school. There he did quite well and by the age of 8 years he could hold a conversation. At the age of 12 years he had only recently learnt to read and write, and to do simple arithmetic. There was no behavioural problem.

EXAMINATION. The typical telangiectasis involved the area of the ophthalmic division of the left trigeminal nerve, and the right side of the face was a little smaller than the left. His speech was normal. The optic fundi were normal, but a right homonymous hemianopia was present. There was a slight right lower facial weakness. The right limbs were slightly shorter than the left, and were also somewhat weak and spastic, but he could grip with his hand and had some individual finger movements. There was only slight weakness of the right leg, the muscle power being about 80% of normal. The tendon jerks were equal on the two sides, but the right plantar response was feebly extensor. Light touch and pain sensibility were normal on each side, but he had astereognosis in his right hand and two-point discrimination was unreliable. He walked well, but he was noticed to plant the right foot on the ground more firmly than the left. His intelligence rating on the Wechsler-Bellvue full scale was 57 (A. R. Dabbs).

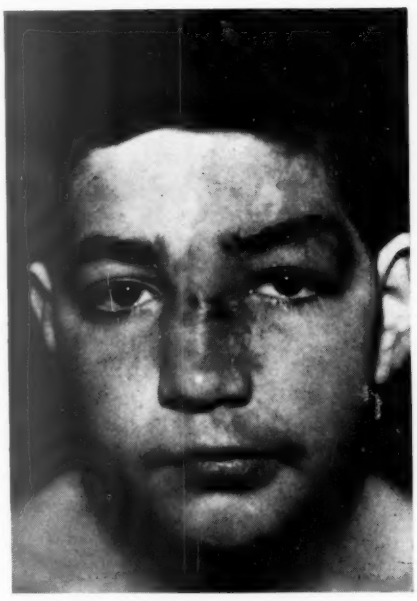

FIG. 20.—Case 5, showing naevus.

INVESTIGATION. Skull radiographs showed that the left hemicranium was much smaller than the right, but the calcification indicative of Sturge-Weber disease was only present in a small area at the left occipital pole (Fig. 21). Pneumoencephalography, however, showed

FIG. 21.—Case 5, radiographs (Towne's projection) showing characteristic calcification present at only a small area at left occipital pole (arrow).

that although the ventricular system was of normal size, the left cerebral hemisphere was shrunken with considerable pooling of air in its subarachnoid spaces (Fig. 22). Electroencephalography showed a 'gross reduction of both normal and barbiturate fast rhythm throughout the whole left hemisphere. A large amount of bilateral subcortical activity was seen better in the right side than the left. A few independent spikes were seen in the left frontal areas and occasionally on the right' (D. Hill).

OPERATION. A left-sided hemispherectomy was performed on July 17, 1956. The whole surface of the left cerebral hemisphere was seen to be covered by an angiomatous malformation similar to our previous cases. Electrocorticography revealed poor activity over the posterior two-thirds of the hemisphere with relatively normal activity in the frontal region, where occasional spike discharges were seen (G. Pampiglione).

PATHOLOGY. Although the surface of the cerebral hemisphere presented an evenly distributed flushed appearance of the cortex and leptomenginges (Fig. 23), radiographs of the specimen disclosed calcification only

FIG. 22.—Case 5, antero-posterior air encephalogram showing shrunken left cerebral hemisphere with capacious subarachnoid spaces.

at the occipital pole (Fig. 24). Dr. Barbara Smith reported on a block from the parietal lobe as follows:

> 'The thickened pia-arachnoid was full of large vascular spaces with thin collagenous walls. These spaces did not involve the nervous tissue itself. There were an increased number of astrocytes in the cortex, particularly in the superficial layers, and considerable submarginal gliosis. Some of the neurones showed ferruginous incrustation. There was only a small amount of calcium in the cortex.'

PROGRESS. The postoperative course has been smooth, and he has not subsequently had any further fits during the three year follow-up period. At first, however, his right hemiparesis was markedly increased, and during the first two weeks there was very little voluntary movement in either the right arm or the right leg. Also there was some questionable dysphasia, while sensibility to touch and pinprick was impaired on the right side. Thereafter, however, there was a gradual improvement in power and sensation, so that six weeks after operation, when he was discharged, he could walk again. At that time he had some voluntary movement of the shoulder and elbow, but none of the wrist and fingers. Power at the right hip and knee was approximately 30% of normal, but there was a foot drop. Sensibility had returned to its preoperative level. Psychological testing now gave an I.Q. of 70 on the Wechsler scale, but it was thought that this apparent improvement was not statistically significant and might be the result of practice. The E.E.G. was flat on the left, and showed normal alpha rhythm on the right side. A short burst of wave and spike activity was seen on over-breathing (D. Hill). The most recent intelligence quotient on the W.I.S.C. scale is 66 (D. Shalman). The patient had commenced work as a messenger boy.

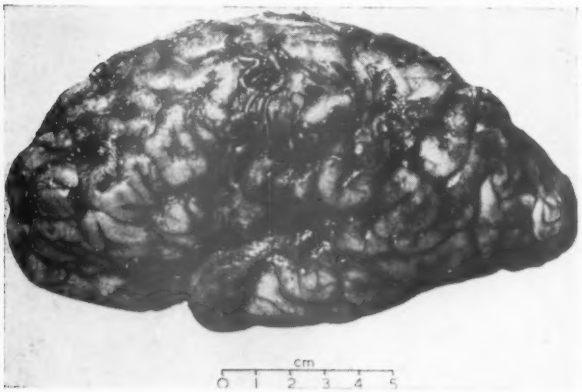

FIG. 23.—Case 5, view of resected hemisphere showing diffuse vascularity of the pia-arachnoid.

FIG. 24.—Case 5, radiograph of specimen showing characteristic calcification only at occipital pole.

Discussion

These five cases are all well marked examples of Sturge-Weber disease, the essential abnormality of which is the congenital lepto-meningeal venous angioma. Our cases conform to the excellent recent descriptions of pathological data given by Medoc *et al.* (1953-54), by Lichtenstein (1954), by Wohlwill and Yakovlev (1957), and by Norman (1958). The angioma brings about a progressive destruction of the cerebral cortex, and the clinical effects depend upon the location of the damage and the rapidity with which it occurs. It does not lead to an intracranial bruit.

The case histories of our patients are typical of the more advanced cases of this condition and the

TABLE

SUMMARY OF RESULTS OF OPERATION

Case No.	Clinical Features at Time of Operation					Clinical Features at Time of Follow-up			
	Age (yrs)	Sex	Laterality of Affected Hemisphere	Epilepsy	Behaviour	Duration of Follow-up (yrs)	Epilepsy	Behaviour	Intelligence
1	3½	M	Left	Several attacks daily	Sullen	8	Fit-free	Sociable	Improved, educable
2	6	F	Left	Two to three attacks per week	Frequent temper tantrums	7½	Fit-free	Sociable	Improved, educable
3	3½	F	Right	Fits had ceased during infancy	Frequent temper tantrums	5	Fit-free	Sociable	Improved, educable
4	16	M	Left	Fits every month	Frequent temper tantrums	3	Fit-free	Satisfactory	Still grossly defective
5	12	M	Left	Several attacks daily	Normal	3	Fit-free	Still normal	Improved, educable

salient features are summarized in the Table. At birth the infant appears quite normal apart from the unilateral facial telangiectasis. After a varying period, in our cases from 3 weeks to 9 months, the child begins to have epileptic seizures which initially involve the side of the body contralateral to the naevus. Later they may spread to the other side as well. The frequency and severity of the fits vary widely. At about the same time as the fits commence, the limbs in the side opposite to the naevus are noted to be weak. This weakness apparently increases as the child grows, and may develop into a marked infantile hemiplegia with wasted shortened and spastic limbs. Further, as the child grows older, mental backwardness becomes evident, and temper tantrums and other behaviour disorders may make their appearance. The characteristic calcification seen in radiographs may be absent in early infancy, and not appear until later. The combination of epilepsy, backwardness and unmanageability may make institutional care necessary. All five of our cases had both facial naevus and infantile hemiplegia. Cases 1, 2 and 4 exhibited the most complete clinical pictures: Case 3 had only a transient epilepsy, but a persistent personality disorder, and Case 5 had epilepsy but a normal personality.

Our cases also illustrate well the value of radiology in this condition, a topic which has recently been intensively reported by Poser and Taveras (1957). All five cases showed marked hemicranial atrophy with a shrunken cerebral hemisphere, which was well outlined in four of the cases by the characteristic calcification and in all five cases by pneumoencephalography. In two cases (Case 1 and 2) calcification was not noted in the skull radiographs taken in infancy, but was markedly developed by the third year of life. Poser and Taveras (1957) also remark on this. In Case 5 the calcification was detectable only in the occipital pole even although the angioma was widespread. Carotid angiography was performed in only two of our cases, both during infancy, and no vascular abnormality was noted. Such a negative finding (except for evidence of hemicranial atrophy) agrees with the usual consensus of opinion (Moniz and Lima, 1935; Bergstrand, Olivecrona and Tönnis, 1936; Riechert, 1943). However, Poser and Taveras (1957) point out that in many cases the presence of the capillary-venous angioma can be disclosed by serial angiography, and that other lesions such as arterial thromboses and external carotid artery anomalies may be disclosed. Only one case with a cirsoid arteriovenous malformation appears to have been reported. None of our cases had suffered from intracranial haemorrhage, although instances both of subarachnoid haemorrhage and of subdural haemorrhage have been reported in this condition (Cushing, 1906; Poser and Taveras, 1957).

There are still comparatively few case reports in the literature of operative intervention for Sturge-Weber disease. Balado (Dimitri and Balado, 1933) performed a craniotomy under local anaesthesia in 1930 on Dr. Dimitri's patient, then aged about 20 years, exposing a cirsoid venous angioma which he treated by electrocoagulation of the principal surface vessels without any alteration in consciousness. Subsequently the patient continued to have attacks, but with a reduced frequency. Krayenbühl *et al.* (1957) state that Tönnis, in 1934, tried the same procedure, but did not describe the results.

A few neurosurgeons report cases in which the Sturge-Weber malformations appear to have been localized to a small part of the cerebral hemisphere

which was then excised, apparently with benefit. Thus Broager and Hertz (1949) report the case of a 5-year-old boy in which the left premotor region was excised largely on E.E.G. evidence. There was a naevus of the face and a naevus on the inner side of the dura in the premotor region, while a number of fine tortuous vessels were noted in the pia of the affected region. The patient was followed up for one year, and was free of fits, but still on anticonvulsive medication. Other surgeons who have reported comparable cases include Green, Foster and Berens (1950), occipital lobe with characteristic calcification; Huber and Zweymüller (1954), parietal lobe; and Krayenbühl *et al.* (1957), temporal lobe. However, a recurrence of epilepsy can follow upon these limited excisions (Krayenbühl, 1959).

Cairns and Davidson (1951) record the first case successfully treated by hemispherectomy. This was a 7-year-old girl with infantile hemiplegia, fits and behavioural disturbances. One year later she was free of fits, her intelligence quotient had risen from 63 to 73, and she appeared educable. Polani (1952) in the following year, gave a preliminary report on the first two cases included in this present paper. Obrador Alcalde (1958), in a recent paper, mentions that other cases have been successfully operated on by Paillas and by McKissock (Laine and Gros, 1956), by French *et al.* (1955), and by Goodall (1957), and he adds a sixth case report from his own experience. This was an 11-year-old patient observed to be free from fits 14 months after the operation.

A recent report from the Mayo Clinic (Peterman *et al.*, 1958) mentions that operation was carried out in four of 35 cases seen in the period from 1935 to 1956. Three of these cases had been submitted to a lobectomy rather than to a hemispherectomy with relief of seizures in one case. The fourth patient had undergone a craniotomy, but the lesion was not extirpated because of the extent of the angioma. Of the 35 cases, 31 had had adequate follow-up studies, and these showed the variability which is encountered in the course of this disease; 17 of the patients were considered well, and two had never had a convulsion; 15 had continued to have seizures, some, however, infrequently. One other of their patients had undergone a cortical excision elsewhere with a successful result. Four patients had died, one after craniotomy and three after progressive deterioration at ages between 9 months and 7½ years. Ten patients had done poorly, five being confined to institutions. Of the 17 patients who had done well, only three showed mental retardation. One indeed had graduated from college, and several were married and rearing families.

The drastic procedure of cerebral hemispherectomy or the less severe one of lobectomy are therefore justified only when there is a proper indication, i.e. disabling epilepsy and/or a personality disorder. If the angiomatous lesion is circumscribed in the brain, a local extirpation may be all that is necessary (Broager and Hertz, 1949), but, if it is widespread throughout one cerebral hemisphere, removal of that hemisphere is indicated.

Our cases show that provided the other hemisphere is structurally normal, hemispherectomy may be confidently expected to abolish the seizures and produce a real improvement in the personality. The infantile hemiplegia is not improved, and subsequent operative procedures may prove necessary to correct a talipes equinus. The patient remains backward, but his intelligence as rated by the usual tests may improve a little even in relation to his increased age, and he may function as a high-grade mental defective and be educable. Thus it has led to improvement in learning in all four of our patients who were operated upon during childhood. It did not benefit Case 4 who was operated upon as an adult. Our experience in all these respects is in agreement with the results of hemispherectomy performed for other types of infantile hemiplegia (Krynauw, 1950).

Before the operation is undertaken, the condition of the other hemisphere is checked by pneumoencephalography and electroencephalography. Pooling of air over the surface in dilated subarachnoid spaces or ventricular dilatation on the supposedly good side indicates damage to it. The electroencephalographic findings need to be interpreted with caution. Krynauw (1950) demonstrated in his cases of infantile hemiplegia that E.E.G. abnormalities in the good hemisphere often cleared up after removal of the diseased one. This may explain both the postoperative improvement in personality and in intelligence.

Given proper indications, the operation is well worthwhile, and the question arises as to the best stage at which it should be performed. An opinion in this respect is largely based on theoretical premises. We have no evidence to suppose that it will benefit a child with infantile hemiplegia but without epilepsy or a personality disorder. If, however, one or both of these is present (and in our cases they had all appeared within the first year of life), the child should be operated on at an early stage in order to stop the seizures and improve learning capacity. The skull of a young infant, however, because of its flexibility, makes the closure

of a large craniotomy difficult. The youngest age at which operation was performed in this series was 3½ years, and no great difficulty was encountered. On theoretical grounds the child could have been operated on with equal ease between the ages of 2 and 3 years, which is probably the preferable age period. As in other conditions causing infantile hemiplegia, aphasia does not appear, even when the left cerebral hemisphere is removed (Krynauw, 1950).

Summary

The case histories of five patients with advanced Sturge-Weber disease (encephalotrigeminal angiomatosis) are recorded. All exhibited epilepsy and/or a behavioural disturbance occurring in association with an infantile hemiplegia and their epilepsy and personality conditions were improved by excision of the affected cerebral hemisphere (hemispherectomy), but not their infantile hemiplegia. All remained mentally backward, but the four who were operated on during childhood proved to be educable. These findings conform to the observations made by others who have performed hemispherectomy for this condition.

We wish to thank the various physicians who have referred us their cases. In particular we are grateful to Dr. P. R. Evans, Mr. P. H. Schurr, Professor P. M. Daniel, Dr. A. L. Woolf, and Dr. Barbara Smith who have helped us with the text, and the various psychologists who have given us their reports. The radiographs were provided by Dr. R. D. Hoare. We are also grateful to the Medical Research Council for a grant towards the investigation of patients with epilepsy treated by surgery which has made the follow-up possible.

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COMPARISON OF CHANGES IN SERUM PROTEINS DURING EARLY TREATMENT IN KWASHIORKOR AND MARASMUS

BY

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Kwashiorkor and marasmus are the two commonest forms of infant malnutrition found in tropical countries and the fundamental aetiological difference between them appears to be in the proportion of carbohydrate in the diet. The diet leading to marasmus seems to be reasonably balanced though insufficient in quantity and therefore in calories as well as protein, whereas the diet leading to kwashiorkor is imbalanced in that there is a protein deficiency but a relative excess of carbohydrates which can lead to an adequate calorie intake. The clinical picture in these two types of malnutrition is strikingly different. Though protein deficiency in the aetiology of kwashiorkor has been emphasized, and without doubt is present in these infants, perhaps insufficient attention has been paid to the carbohydrate metabolism in kwashiorkor. Before going so far as to suggest that the clinical signs of kwashiorkor are related to a relative excess of carbohydrate, and that it is this excess which gives rise to the oedema, skin and hair changes and fatty liver, either directly or indirectly, seen in kwashiorkor and not in marasmus, it was thought that a comparison of the protein metabolism in the two states might show whether in fact protein metabolism differed in the two conditions. If a difference is present, then one can, with more justification, designate kwashiorkor as protein malnutrition; if there is no difference, apart from that of degree, then it is possible that kwashiorkor is no more nor less dependent on protein malnutrition than is marasmus and the emphasis in aetiology should perhaps be shifted to carbohydrate.

A simple approach to this problem lies in the study of the serum proteins, and especially in the first few days of treatment when the body is faced with the possibility of repairing the damage in the protein metabolism. It can be assumed that those parts of the protein 'workshop' most severely disorganized by the previous state of protein shortage, and possibly imbalance, would respond to treatment at a rate different from that of the less severely affected mechanisms and this might be reflected in the serum protein levels in the early days of treatment.

Methods

There are many cases which show some signs of kwashiorkor and of marasmus, the so-called marasmic kwashiorkor, but in this study cases were deliberately chosen which were as near the extremes as possible so that the kwashiorkor group all had hair and skin changes and gross oedema, whilst the marasmic group had none of these signs. The mental state, the apathy of the kwashiorkor, was present in all the cases studied, whereas in the marasmic group all the children on admission had a noticeable mental alertness, being very interested and apprehensive of their surroundings. Though liver biopsy was not done, the cases were clinically distinct and of one type of malnutrition or the other.

The children were all aged 1 to 4 years inclusive.

Approximately 2 ml. of blood were taken before treatment commenced and on each subsequent morning until the 14th day in hospital. The blood was allowed to clot and the serum decanted off. After centrifugation the total serum proteins were estimated by refractometry and then subjected to paper electrophoresis. The proportion of protein present was assessed by measuring the density of the various protein bands.

The treatment given to the patients was not controlled in any way, it being left to the clinician in charge to give drugs, etc., according to clinical needs. However, the composition of the diet for kwashiorkor was standard and consisted mainly of whole powdered milk, with casein and sugar until the sixth day, after which vegetables, meat, fish, etc., were added. The diet of the marasmic cases was qualitatively the same as the kwashiorkor.

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Results

Kwashiorkor. The various protein fractions in the serum as determined daily are expressed both as g. % and as percentages of the total serum proteins. The results are seen in Table 1 and Figs. 1 and 2 and represent the means of seven cases.

The pre-treatment values reported here were lower for albumin and the increase in the albumin in response to treatment was not so striking as reported by Davin (1955). This slower rise is presumably because protein hydrolysate is not now added to the diet as it was when Davin carried out his studies in the same hospital.

The alterations seen in the percentage of the various fractions in kwashiorkor at the commencement of treatment are not all to the same degree when compared with the mean values of a series of 41 normal African children (Table 2). In contrast to the albumin fraction which is lower, the α_1 and γ globulin percentages are higher, whilst the α_2 and β remain approximately the same. The drop in total proteins, however, is such that all fractions

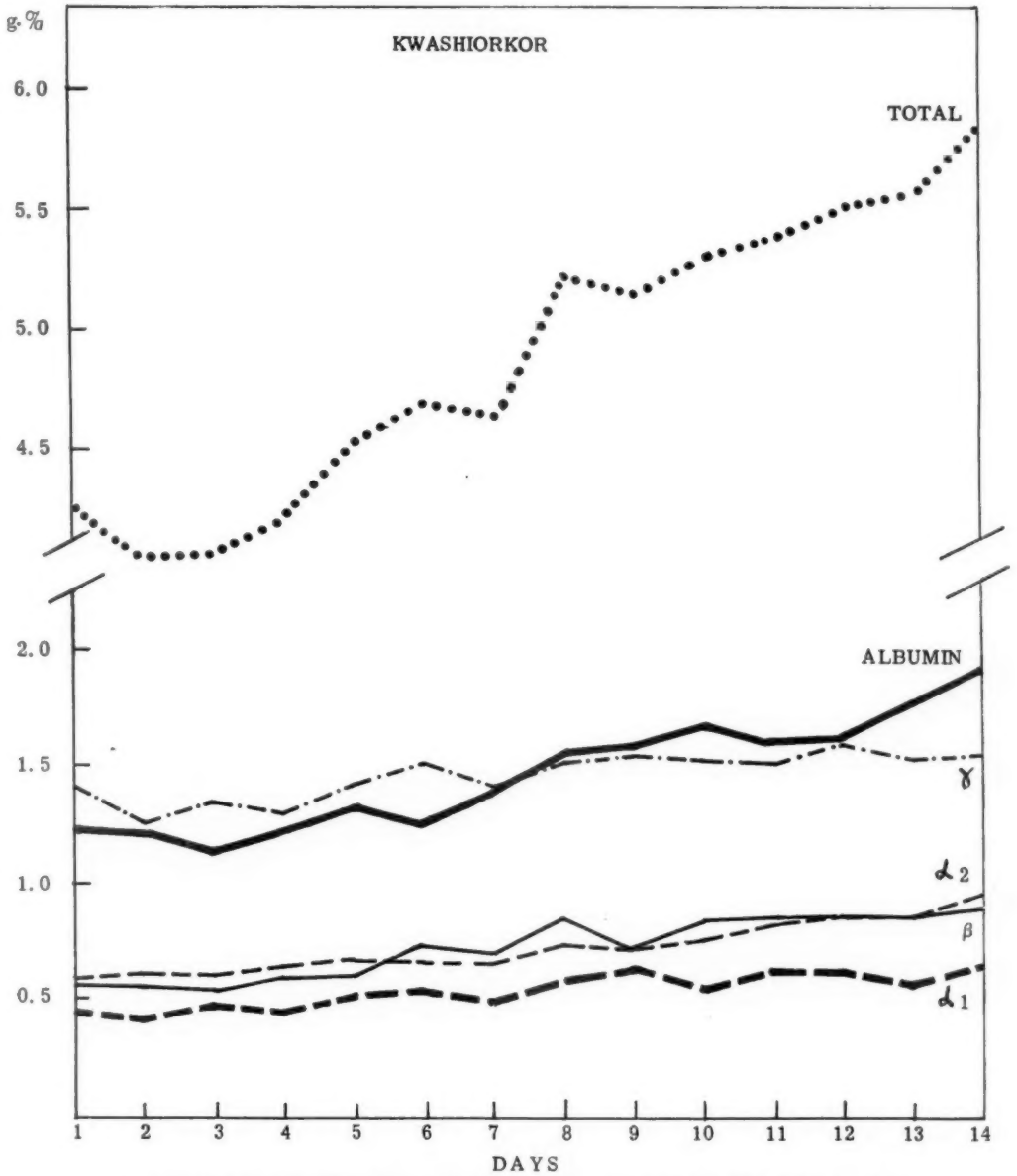

FIG. 1.—Mean g. % values for serum protein fractions during early treatment in kwashiorkor.

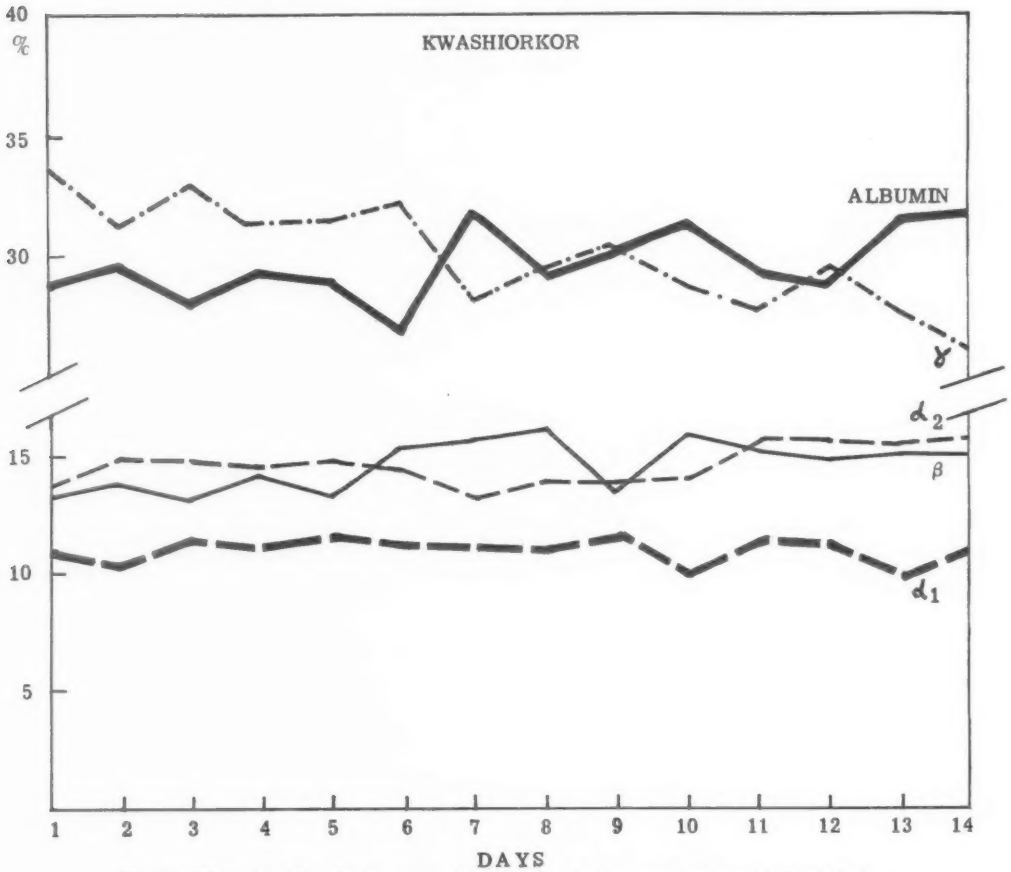

FIG. 2.—Mean % values for serum protein fractions during early treatment in kwashiorkor.

when expressed as g. % are lower in value, though less obviously so in α_1 and β globulins.

The total proteins increase during treatment at a fairly constant rate except for a slight reduction in the first two days of treatment. This may be due to increased blood volume consequent upon the removal of oedema fluid, and rehydration therapy.

It can be seen that the proportion of albumin tends to rise ($p = 0{\cdot}05$), whilst the α_1 globulin is

TABLE I
MEAN DAILY VALUES OF SERUM PROTEINS IN CASES OF KWASHIORKOR

Day	Total Protein (g. %)	Albumin (g. %)	α_1 g. %	α_2 g. %	β g. %	γ g. %	Albumin (%)	α_1 %	α_2 %	β %	γ %
1	4·26	1·23	0·46	0·59	0·56	1·42	28·8	10·8	13·7	13·2	33·5
2	4·04	1·21	0·42	0·60	0·56	1·25	29·5	10·3	14·8	13·9	31·4
3	4·06	1·12	0·47	0·60	0·53	1·34	27·9	11·4	14·7	13·1	32·9
4	4·19	1·22	0·46	0·61	0·60	1·30	29·3	11·1	14·4	14·1	31·1
5	4·51	1·31	0·52	0·67	0·60	1·41	28·8	11·6	14·8	13·3	31·4
6	4·70	1·26	0·53	0·67	0·73	1·51	26·8	11·2	14·4	15·4	32·1
7	4·64	1·38	0·49	0·67	0·69	1·41	31·9	11·2	13·2	15·6	28·0
8	5·24	1·56	0·58	0·74	0·86	1·53	29·2	11·1	14·0	16·2	29·4
9	5·17	1·59	0·61	0·71	0·71	1·55	30·1	11·8	13·9	13·5	30·6
10	5·33	1·67	0·53	0·76	0·84	1·53	31·4	10·0	14·1	15·7	28·8
11	5·40	1·59	0·62	0·84	0·85	1·50	29·3	11·5	15·7	15·5	27·9
12	5·54	1·62	0·61	0·86	0·85	1·60	28·7	11·2	15·7	15·0	29·4
13	5·60	1·79	0·55	0·86	0·87	1·53	31·5	9·9	15·6	15·3	27·7
14	5·93	1·91	0·64	0·94	0·90	1·54	31·8	11·0	15·9	15·1	26·2
P	0·001	0·001	0·001	0·001	0·001	0·001	0·05	0·05	0·05 –0·025	0·025 –0·01	0·001
Normal Values	7·37	3·28	0·57	0·97	0·92	1·62	44·5	7·8	13·2	12·5	22·0

TABLE 2

MEAN % OF VARIOUS SERUM PROTEIN FRACTIONS IN SEVEN CASES OF KWASHIORKOR AND SEVEN CASES OF MARASMUS AND IN A NORMAL SERIES (DAVIN, 1955)

	Albumin	Globulin			
		α_1	α_2	β	γ
Kwashiorkor ..	28·8	10·8	13·7	13·2	33·5
Marasmus ..	36·0	10·8	12·8	11·5	28·9
Normal	44·5	7·8	13·2	12·5	22·0

TABLE 3

CHANGE COMPARED WITH NORMAL IN VARIOUS FRACTIONS OF SERUM PROTEINS AT COMMENCEMENT OF TREATMENT EXPRESSED AS % RISE OR FALL FROM NORMAL

	Kwashiorkor	Marasmus
Albumin	−62	−39
α_1	−19	+ 5
α_2	−39	−30
β	−39	−32
γ	−12	− 4

constant. The α_2 globulin rises ($p = 0{\cdot}05$-$0{\cdot}025$) as does the β globulin ($p = 0{\cdot}025$-$0{\cdot}01$), whereas the γ fraction falls ($p = 0{\cdot}001$) in the first 14 days of treatment. These changes are reflected in the results expressed as g. % except for the γ globulins where a rise is now seen, and in the α_1 fraction where the constant percentage means that with an increasing total serum protein the g. % of this fraction shows a rise.

Davin (1955) carried out serum electrophoresis before treatment and after seven to 12 days of treatment in cases of kwashiorkor and his results showed the same proportional tendencies with treatment as those reported here, though there are slight differences in the actual values in the two groups.

These results compare favourably with those of Autret and Behar (1954) but as these authors do not separate the α globulins in their control sera it cannot be seen if they also found a rise in α_1 globulin.

The relative fall in the level of each serum protein component in kwashiorkor, compared to normal, is not constant. In the present seven cases the mean albumin level was 62% lower, and the α_2 and β 39%, α_1 19% and γ 12% lower than Davin's normal figures (Table 3) (Davin, 1955). The reason for this is not known, but it must reflect different metabolic activities in the various serum proteins, though whether these are based on supply or demand cannot appear from this study.

Marasmus. The results of the serum protein changes in the first 14 days of treatment in marasmic infants are seen in Table 4 and Figs. 3 and 4. There are some differences when compared to the kwashiorkor group at the commencement of treatment, mainly in the total serum protein level which is not so low in the marasmics, largely as a result of the higher albumin level in these cases.

As with kwashiorkor, the changes in the relative levels of the serum protein components are not constant (Table 3). The albumin level was 39% below normal, the α_2 and β fell approximately 35% and the α_1 and γ showed little change.

Hence in these two conditions of infant malnutrition the α_2 and β seem to be linked and equally affected, whereas the reduction in albumin, similar to that in α_2 and β in marasmus, is much more marked in kwashiorkor, the least proportional changes being seen in the α_1 and γ globulins.

If the rate of increase in the g. % of each of the serum proteins in the kwashiorkor and marasmus groups is compared it is found that all the serum

TABLE 4

THE MEAN DAILY VALUES OF SERUM PROTEINS IN THE CASES OF MARASMUS

Day	Total Protein (g. %)	Albumin (g. %)	α_1 g. %	α_2 g. %	β g. %	γ g. %	Albumin (%)	α_1 %	α_2 %	β %	γ %
1	5·45	1·99	0·60	0·68	0·63	1·55	36·0	10·8	12·8	11·5	28·9
2	5·29	1·89	0·49	0·73	0·64	1·54	35·5	9·3	13·9	11·8	29·5
3	5·30	1·84	0·48	0·74	0·64	1·60	34·7	9·3	13·9	11·8	30·3
4	5·45	2·00	0·48	0·73	0·64	1·60	36·7	9·0	13·3	11·5	29·5
5	5·50	2·00	0·54	0·73	0·63	1·60	36·3	9·9	13·2	11·4	29·3
6	5·49	1·97	0·48	0·74	0·64	1·66	36·1	8·8	13·4	11·4	30·2
7	5·66	2·12	0·48	0·76	0·70	1·60	36·0	8·7	13·9	12·3	29·1
8	5·68	2·11	0·48	0·73	0·70	1·66	37·3	8·5	12·8	11·9	29·4
9	5·79	2·19	0·49	0·71	0·71	1·69	37·7	8·5	12·4	12·1	29·2
10	5·79	2·18	0·47	0·74	0·73	1·67	37·7	8·2	12·8	12·5	28·8
11	6·05	2·28	0·54	0·83	0·71	1·69	37·5	9·0	13·7	11·6	28·1
12	6·13	2·39	0·55	0·78	0·76	1·65	38·5	9·2	13·0	12·3	27·0
13	6·10	2·40	0·52	0·79	0·74	1·65	38·9	8·7	13·0	12·1	27·3
14	6·39	2·38	0·51	0·86	0·85	1·79	37·1	8·1	13·7	13·1	28·1
P	0·001	0·001	0·1	0·005 −0·001	0·001	0·001	0·005	0·01 −0·005	0·5	0·01 −0·005	0·005 −0·001

proteins increase at a greater rate in kwashiorkor than in marasmus except for the γ globulins, whose rate of change is the same.

Discussion

The similar serum protein pattern found in kwashiorkor and marasmus suggests that the protein metabolism in both types of malnutrition differs only in degree, and that marasmus is as much a protein malnutrition as is kwashiorkor. Its more rapid response to treatment supports the view that kwashiorkor is a more acute form of malnutrition than marasmus, though it is difficult to comprehend how rate of onset can influence rate of response to treatment.

In both kwashiorkor and marasmus there is a deficiency of adequate protein intake and the pattern of the serum proteins is the same in each except that the reduction in serum albumin is greater in kwashiorkor. The apparent link, in the extent of the change from normal between α_1 and γ globulins and between α_2 and β globulins in both con-

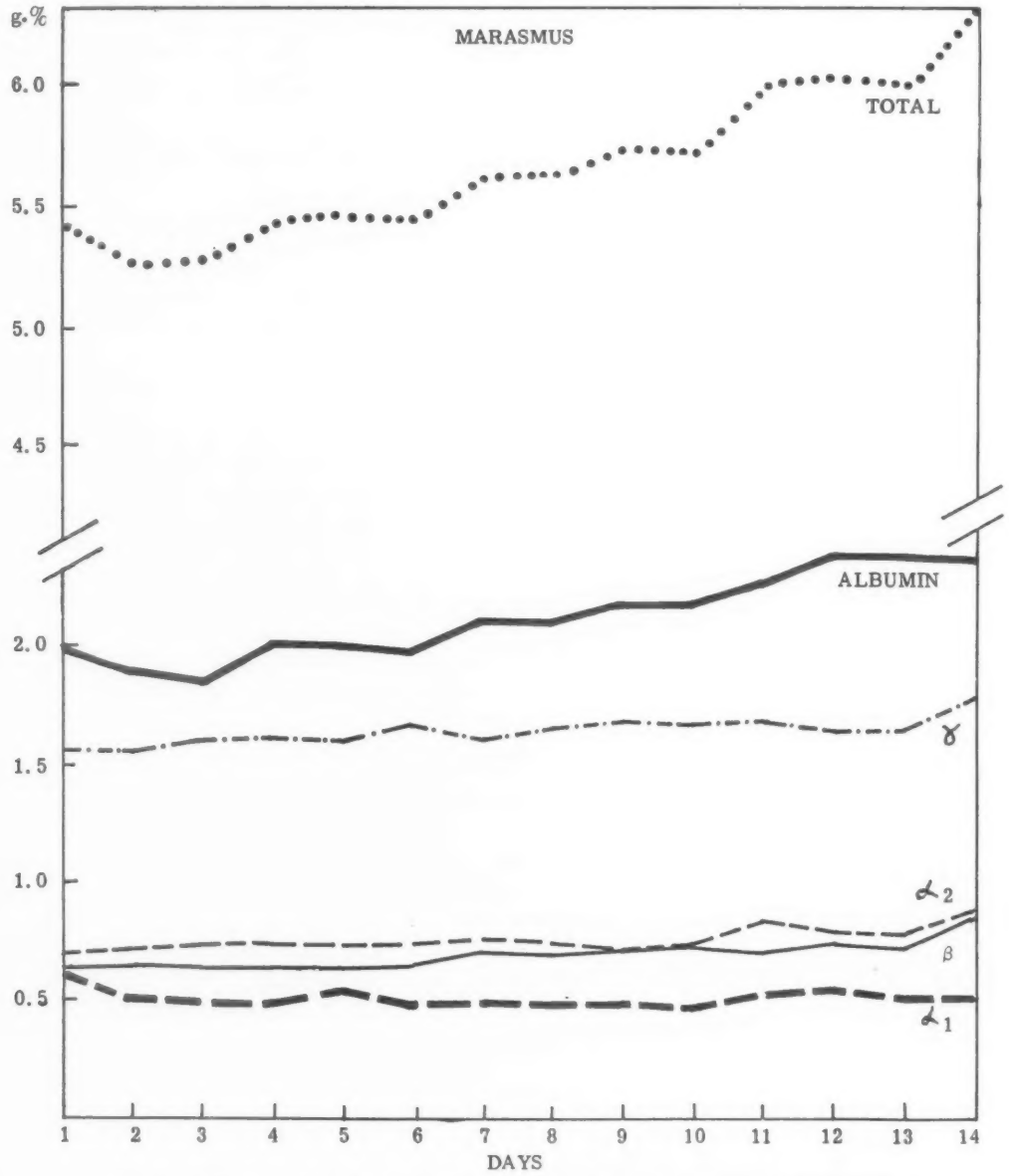

FIG. 3.—Mean g. % values for serum protein fractions during early treatment in marasmus.

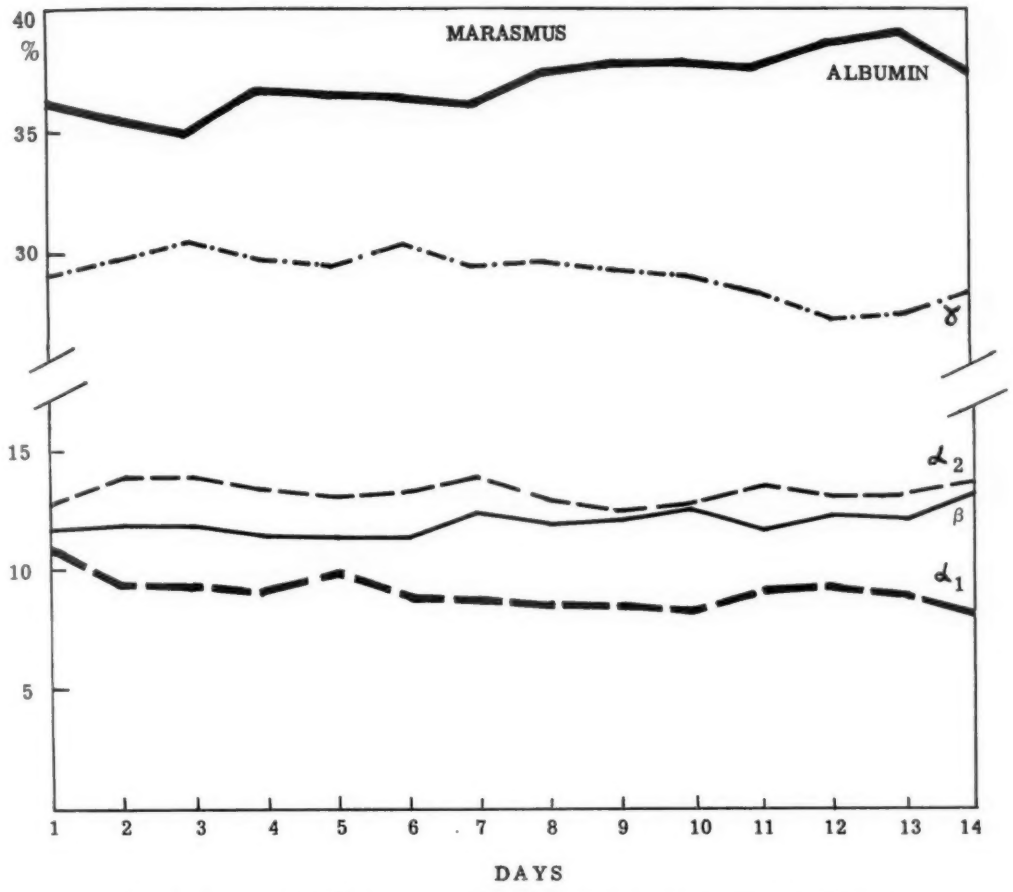

FIG. 4.—Mean % values for serum protein fractions during early treatment in marasmus.

ditions, suggests a common error in protein metabolism because these proteins are not equally affected in this way in other diseased states. If one assumes that the protein metabolism in the two conditions is affected in a similar way, and that there is no reason why protein metabolism should be different in these two types of infant malnutrition which have in common a deficient intake of adequate protein, then the clinical differences must be due to some factor other than protein.

The main difference in the diet leading to these two types of malnutrition is a relative excess of carbohydrate in the pre-kwashiorkor intake. As it is suggested that protein metabolism is similar in these two kinds of malnutrition, then it is possible that at the clinical picture of kwashiorkor is due, not solely to protein malnutrition but to a relative excess of dietary carbohydrate (Macdonald, 1960).

The rate of protein recovery is more rapid in kwashiorkor. The γ globulin shows little fall in either condition and the response to treatment is similar, and it is possible that the γ globulin has not to any extent been influenced by the inadequate protein intake but only by the infection contracted by the child.

An interesting feature in these results is the apparently close relationship between α_1 and γ globulin and between α_2 and β globulin. The extent of the fall in each pair as well as the rate of response to treatment is similar. This suggests that the metabolic processes concerned in the production and utilization of these two pairs of serum proteins are closely allied.

These results therefore show that before the commencement of treatment the pattern of change in the serum proteins in kwashiorkor and marasmus is similar. The serum protein response to an identical diet is also similar in the two conditions, the differences being in degree only. Thus no evidence can be found in this study to suggest that protein metabolism is qualitatively different in kwashiorkor from that in marasmus.

Summary

Daily serum protein electrophoresis for the first 13 days of treatment in seven cases of kwashiorkor and seven cases of marasmus reveals no difference qualitatively in serum protein response to a diet which was similar in all cases.

It is suggested that the protein metabolism in kwashiorkor is similar to that in marasmus, and that the clinical differences found between the two conditions are due to some other factor, possibly the relative excess of dietary carbohydrate.

I am grateful to the Ciba Foundation and the National Institut d'Hygiene for the award of a bursary which enabled me to visit Dakar. I also wish to express my sincere appreciation to Professcr J. Sénécal and his staff in the Service de Pédiatrie, Hôpital A. le Dantec. Dakar, for every assistance in carrying out this work.

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HIGH PROTEIN FEEDING IN KWASHIORKOR*

BY

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The highly satisfactory results with skimmed cow's milk in the treatment of uncomplicated kwashiorkor are well documented. Dean (1953) stated that a patient needed 50 g. protein daily, but in 1956 recommended that fat be added as well. It has been suggested that very high protein intake, by supplementing cow's milk with concentrated powdered milk protein, may hasten the cure of the disease. Many hospitals still use this expensive therapy. Pretorius, Hansen, Davel and Brock (1956), however, did not observe benefit from supplementing skimmed milk, and it has also been suggested that too high a protein diet may cause harm and even sudden death (Gyorgy, 1955; Sénécal, 1958).

It was therefore decided to study this problem as part of an investigation, initiated in November, 1957, into anaemia in kwashiorkor (Walt, 1959). Alternate cases were given a protein supplement and a comparison of the total daily protein and caloric intake, daily weight change and weekly serum protein estimations in cases in each group was undertaken.

Material and Methods

Six hospital beds were made available for the study and as each bed became vacant, a new patient with kwashiorkor was admitted to the trial. All the patients were ill, necessitating admission to hospital. Many had superimposed infections.

A full clinical examination was carried out on every patient by the first author, and, without his prior knowledge, allotted alternately to the two treatment groups.

From November 22, 1957, to June 29, 1958, 45 patients were admitted to the trial. Five patients in each treatment group died, leaving 35 cases for analysis. These cases were observed for 28 days.

Treatment Groups. Skimmed lactic acid milk only (SLAM) was administered in 17 cases; skimmed lactic acid milk plus protein supplement (SLAM + PS) was administered in 18 cases.

From July 15, 1958, to June 22, 1959, a further 48 cases, comprising the second series, were admitted. There were 12 deaths; two cases were excluded because of tuberculosis and two cases because of unreliable records. This left 32 cases for analysis. These cases were observed for 42 days: skimmed lactic acid milk, plus injectable iron (SLAM + Fe) was administered from the eighth hospital day to 13 cases; skimmed lactic acid milk plus protein supplement (SLAM + PS) ('Tervamix'), as in the first series to 19 cases.

It will be noted that the only difference between the first and second series of cases was the addition of iron injections after the eighth day to the non-supplemented group. Table 1 shows that the severity of kwashiorkor was similar in both groups, as was the number of patients requiring intravenous therapy and/or blood transfusions. There was a similar proportion of infections in the two groups. The average age for the SLAM + PS group was 18 months and for the other 20 months. All the patients were of African (Bantu) origin. An analysis of the deaths among the total of 93 cases admitted showed that the median days of death in the SLAM group and SLAM + PS groups were the fourth and third days respectively. Statistically there was no significant difference in the death rates of the two groups.

TABLE 1

Cases	Treatment	
	SLAM	SLAM + PS
Cases admitted	46	47
Deaths	14	8
Cases excluded	2	2
Cases analysed	30	37
Mean age (months)	20	18
Severity of illness on admission:		
Mild	9 (30%)	12 (32%)
Moderate	16 (53%)	19 (52%)
Severe	5 (17%)	6 (16%)
Cases requiring intravenous therapy	6	9
Blood transfusions	3	3
Cases with infections:		
In first week	10 (33%)	16 (43%)
During hospitalization	21 (70%)	26 (70%)

Feeding. Lactified skimmed cow's milk (Walt, Wills and Nightingale, 1950) was offered to all patients. They were encouraged and coaxed to drink as much as they wished by the nursing staff, who are taught to be

* Presented at the 1st Congress of the Nutrition Society of Southern Africa on November 16, 1959, at Pretoria.

kindly and patient with these difficult children. The minimum quantities offered for the first three days were 1½, 2 and 2½ oz. per lb. body weight respectively. Full ward diet was introduced on the 15th day.

The alternate patients received a supplement of 'Tervamix', a powder containing 68% milk protein (casein), obtained from skimmed milk. It was added to the lactified milk in the proportion of 1½ g. per lb. body weight, thus providing an extra 1 g. protein per lb. body weight per day.

Additional Routine Therapy on Admission. The following was administered to all patients: procaine penicillin 300,000 units intramuscularly daily for seven days; triple sulphonamide 90 mg. per lb. body weight daily for seven days; vitamin C, 50 mg. daily; potassium chloride, 5 gr. three times per day for seven days; folic acid ('Folvite') 7·5 mg. intramuscularly daily for three days, followed by 5 mg. orally three times per day for 25 days; intramuscular iron ('Imferon'), on the recommended basis, was given from the eighth day to the patients in the second series not receiving protein supplement (SLAM + Fe).

Measurements. All patients were weighed by the paediatric registrar daily just before the 9 a.m. feed, at the same time as the protein supplement was weighed. The daily quantity of feed taken by each patient was accurately measured and recorded allowing the daily protein and caloric intake to be estimated (Fig. 1).

Serum Proteins. Serum protein estimation and electrophoresis were performed on admission and weekly thereafter by the methods of Joubert, Hookins and Hunter (1959).

Results

The addition of injectable iron to the patients in the non-supplemented group in the second series apparently did not affect the protein and caloric intakes, weight changes and serum protein levels materially. Therefore, for purposes of analysis, the results of the non-supplemented groups in the first and second series of cases have been combined and compared with the results of the protein-supplemented cases from both series. Figs. 1, 2 and 3, and Table 2 summarize some of the findings in the two groups.

Response to Treatment. All 67 cases recovered well and were discharged from hospital at the end of the period of observation; many could have been discharged earlier. The patients had their diuresis between the fourth and 12th days; clinical oedema tended to disappear earlier in the protein-supplemented group. By the end of 14 days, the skin lesions were healed and the patients smiling, a sign of recovery which we find very useful; their appetites were good and dispositions happy unless some infection supervened. These infections were a constant source of worry, and in the majority of cases necessitated the use of appropriate antibiotics.

Differentiation between dietetic and infective diarrhoea is admittedly difficult but the former never appeared to be an important cause of illness. Those patients given supplementary protein did not suffer an obvious increase in diarrhoea.

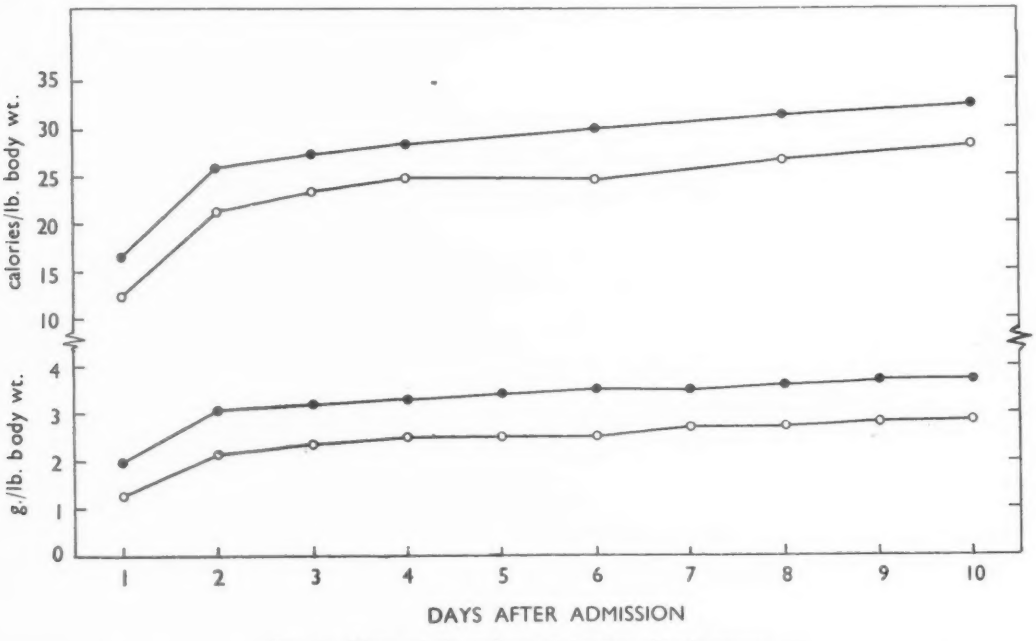

FIG. 1.—Mean calorie and protein intakes of both groups.
O = SLAM: skimmed lactic acid milk; ● = SLAM + PS: skimmed lactic acid milk plus protein supplement.

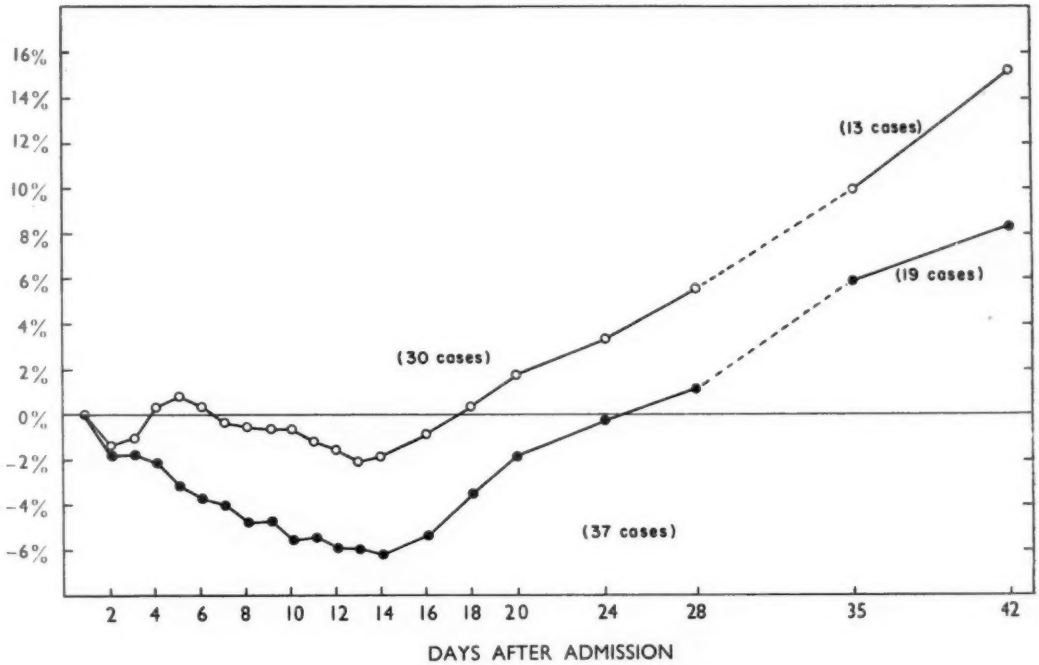

FIG. 2.—Mean percentage change in body weight in both groups.
○ = SLAM; ● = SLAM + PS.

Protein Intake. (Fig. 1.) By the 10th day of treatment the mean protein intake of the SLAM + PS group was 30% more than in the SLAM group (3·7 g. as compared with 2·8 g./lb. body weight).

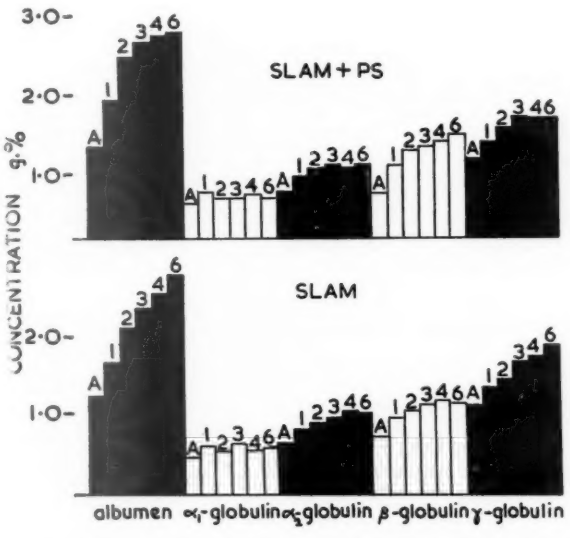

FIG. 3.—Mean serum proteins and fractionation in both groups.
A = on admission; numerals refer to number of weeks after admission.

Caloric Intake. (Fig. 1.) Likewise by the 10th day of treatment the mean caloric intake of the SLAM + PS group was higher than in the SLAM group (32·5 as compared with 28·4 cal./lb. body weight).

Weight Change. The percentage change in body weight (Fig. 2) in the two groups showed that those given protein supplement did not gain as well as those fed skimmed milk only. By the 28th day, the SLAM + PS group was only about 1% above their admission weight, but the SLAM group (without supplement) was 5·6% over the admission weight. This difference was probably significant ($p < 0.05$).

In the second series of cases which were weighed up to 42 days, there was still a difference between

TABLE 2

Cases	Treatment	
	SLAM	SLAM + PS
Mean weight (lb.):		
On admission	19·3	20·0
At 28 days	20·5	20·2
At 42 days	22·4	21·6
Mean protein intake at 10 days (g./lb. body weight)	2·8	3·7
Mean caloric intake at 10 days (cal./lb. body weight)	28·4	32·5

the two groups, but this was no longer significant (Fig. 2).

Serum Proteins. Fig. 3 compares the serum protein levels of the two groups. There was no greater rise in those cases receiving protein supplement.

Discussion

Adequate control groups are essential when a trial of varied treatments is undertaken. In this investigation random allocation of cases resulted in similar age and weight distributions and severity of kwashiorkor in the two treatment groups. Thus the only difference between the groups was the diet.

We have used weight gain, a rise in serum proteins and clinical recovery as the criteria for improvement in the two groups. When observed for only 28 days those patients receiving supplementary protein did not gain as well as those receiving skimmed lactic acid milk only (Fig. 2). When, however, the patients were observed for 42 days, this difference was much less evident. Possible reasons for this difference are the slightly larger number of infections in the first week and the earlier loss of oedema in this group. Alternatively, it may be due to difficulty experienced in metabolizing the extra protein. The amount of protein taken increased daily so that by the 10th day a mean of 2·8 g. per lb. body weight daily was consumed by the control group. This was sufficient to initiate cure as defined by Brock, Hansen, Howe, Pretorius, Davel and Hendrickse (1955). It is felt therefore, that supplementation of skimmed milk with extra protein is unnecessary. This merely confirms the opinion of Pretorius *et al.* (1956), Pretorius and Smit (1958), and Béhar, Viteri, Bressani, Arroyave, Squibb and Scrimshaw (1958).

Sénécal (1958), on the other hand, has recently reported excellent results with partly skimmed milk supplemented by protein hydrolysates, but his conclusions are not supported by a controlled series of patients. He felt that his good results were due in part to the high caloric intake, 25% of which was supplied by protein. His patients took as much as 140 calories per kg. per day. In our patients no attempt was made to increase the calorie intake above that provided by skimmed milk (and extra protein), recovery occurring on 55-65 calories per kg. per day. In patients developing kwashiorkor, it is believed that the calorie intake is adequate but that protein is markedly deficient. In Sénécal's cases, one suspects that some patients were marasmic and deficient in both calories and protein. We realize, however, that the earlier introduction of a ward diet is likely to be of benefit to some patients, and that 14 days on skimmed milk only is probably too long.

We are convinced that infection plays an important part in retarding the recovery of our patients and in the causation of a mild but persistent anaemia, as has already been suggested by Walt (1959). Although it is difficult to assess, we believe that the prophylactic penicillin and sulphonamides used in this trial were of no obvious benefit. We feel therefore that chloramphenicol is probably the drug of choice, particularly in our area where infective enteritis is common.

The total serum proteins and all fractions increased rapidly by the 14th day of the treatment; thereafter they rose only a little more to levels and ratios typical for African patients. We are at variance with Sénécal (1958), who despite a statement that the α_2 globulin decreases, produced a diagram remarkably similar to our Fig. 3. In all our cases this fraction rose steadily and rapidly.

Conclusions

In this series of patients no advantage in weight gain was demonstrated in those receiving protein supplements and therefore higher calorie intake. The minimum quantity of protein, on a body weight basis, necessary for the cure of kwashiorkor has yet to be determined, even though Dean (1953) stated that he had had some good results from as little as 25 g. protein daily. In this series, by the 10th day, 2·8 g. per lb. body weight, representing more than 50 g. protein in the average patient, was consumed and cure was initiated. It is possible that some patients would profit even more by the introduction of a full ward diet as early as the eighth day.

Because infection plays a major role in the early deaths from kwashiorkor, a series of cases receiving a broad spectrum antibiotic prophylactically needs to be studied.

We believe that 'pure' or uncomplicated kwashiorkor responds so well to skimmed cow's milk that these patients should never die. Skimmed milk is very satisfactory and much cheaper than protein hydrolysates or concentrated powdered milk protein, which have not yet been shown to be superior. The rightful place of skimmed milk appears to be as a supplement to the high carbohydrate (starch) diet of the African. Although 'Tervamix' has not been shown in this study to hasten the cure of patients with overt kwashiorkor, it may well be a useful non-bulky high protein supplementary food.

Summary

The treatment of two groups of patients with kwashiorkor is compared. Both received skimmed

actic acid milk but one group was supplemented with concentrated milk protein.

This group did not show any advantage in clinical recovery, weight gain or rise in serum protein levels over the non-supplemented group.

It is concluded that protein supplementation of skimmed milk in the treatment of kwashiorkor is not beneficial.

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THE NATURE OF THE NEONATAL PULMONARY HYALINE MEMBRANE

BY

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Hyaline membranes are seen in the lungs of nearly one-third of prematurely born infants who die after birth at the Royal Women's Hospital, Melbourne. The nature of the membranes has been discussed often in the literature (Farber and Wilson, 1932; Tregillus, 1951; Claireaux, 1953; Bruns and Shields, 1954; Gilmer and Hand, 1955; Lendrum, 1955; Lynch and Mellor, 1955; Stevenson and Laufe, 1955; Gitlin and Craig, 1956 and many others). The subject has also been reviewed by Tran-Dinh-De and Anderson (1953), Curtis (1957), and others, and in an Editorial in the *Lancet* (1958). So far there is no generally accepted explanation of the mode of origin of the membranes and opinions differ widely on the nature of the material of which they are composed. Two main views are held. One postulates an origin from the contents of the amniotic sac and the other from an exudate from the pulmonary capillaries.

The present study is based on observation of morphological changes in affected lungs and was undertaken after a variety of histochemical and interferometric techniques had been employed without significant result. From microscopic examination of the lungs using sections prepared by conventional methods it is concluded that hyaline membranes result from necrosis of epithelial cells in respiratory bronchioles and form *in situ*.

Material

Sections of the lungs have been examined from 133 consecutive cases of hyaline membrane disease occurring in a three-year period and the clinical notes of each case have been reviewed. Necropsy is routine for infants who die and only very rarely is objection made. Approximately 320 autopsies (stillbirths and neonatal deaths) are performed each year. Blocks are taken from the lower lobe of one lung in every case, fixed in formalin and prepared for microscopic examination in the usual way. Sections are cut from one block in each case.

Microscopic Findings. Most hyaline membranes are of a uniform eosinophilic and homogeneous appearance and line air spaces which appear to have been patent at the time of death. The affected air spaces are usually described as alveolar ducts and sometimes as alveolar ducts and alveoli. It is now clear that the alveolar components of the lungs are not involved in hyaline membrane disease and that respiratory bronchioles are the site of hyaline membrane formation.

In sections stained to show elastic fibres the characteristic pattern for respiratory bronchioles is seen around all hyaline membrane affected spaces (Fig. 1). Between affected spaces the lung has a solid structure in which elastic fibres are less frequent, stain faintly and are of irregular distribution. Frequently hyaline membranes are seen lining one side of a respiratory bronchiole while the opposite side is lined normally by cuboidal epithelial cells. In some cases hyaline membranes are seen in longitudinal sections of respiratory bronchioles abutting on the normal columnar lining of terminal bronchioles. Spaces lined by membranes usually have a surrounding lamina propria outside which there are obvious respiratory structures of smaller dimension which are not patent. These are the definitive alveolar tissues in which hyaline membranes do not occur.

In the immature lung of the 1,001-1,500 g. baby the general anatomical features seem to us to be as illustrated in Fig. 2.

T is a terminal bronchiole around which the elastic layer is continuous. R_1 and R_2 are respiratory bronchioles around which the elastic layer is interrupted. A is a site containing potential alveolar tissues which may or may not be functional at this stage of development. Here the elastic fibres have no pattern and are less numerous.

The transition from a terminal to a respiratory bronchiole is abrupt. The columnar cells of the terminal bronchiole give way to much less con-

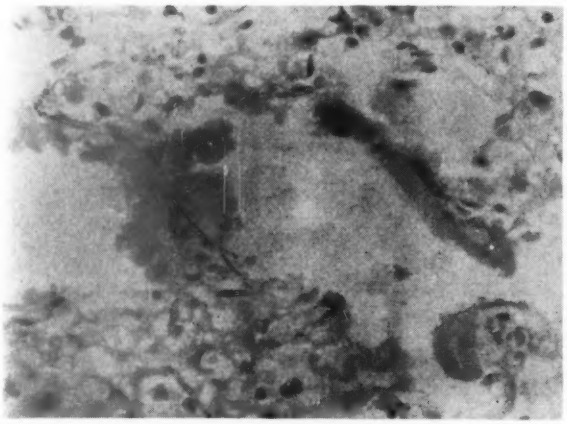


FIG. 1.—Section of respiratory bronchiole showing interrupted pattern of elastic fibres.
(Weigert's elastic stain × 228.)

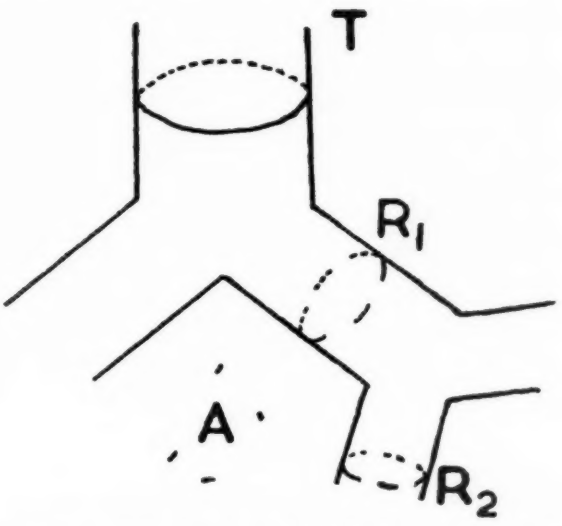


FIG. 2.—Diagrammatic illustration of elastic fibres around bronchioles.

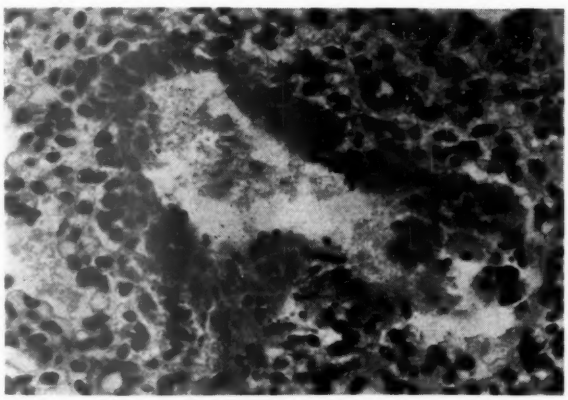
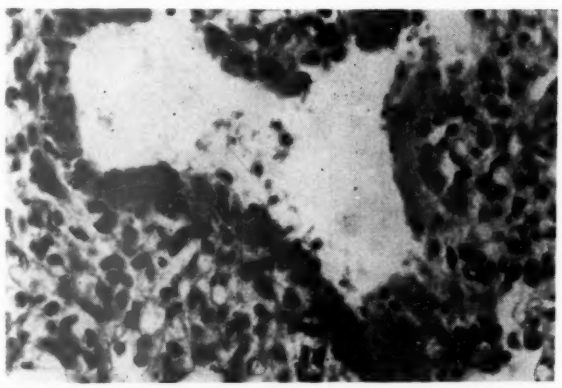


FIG. 3.—Section of respiratory bronchiole lined by partly necrotic epithelial cells.
(H. and E. × 228.)



IG. 4.—Section of respiratory bronchiole showing partly necrotic ithelial cells and a segment of hyaline membrane on the right.
(H. and E. × 228.)

spicuous epithelial cells which are cuboidal or lower. The elastic layer becomes interrupted and the lumen is narrower. The cuboidal cells lining respiratory bronchioles have a clear colourless cytoplasm and a centrally placed round vesicular nucleus.

In 69% of the cases in this series the membranes were not all entirely eosinophilic but contained basophilic particles. In some cases these stained deeply while in others they were just visible. Sometimes the origin of the basophilic particles from the nuclei of epithelial cells was obvious (Fig. 3) mainly because of the regular distribution around the lumen and also because of the size and location of the material in relation to the surrounding eosinophilic membrane. Except when the particles were extremely fragmented there was no possibility of mistaking the appearances for degenerate leucocytes. Appreciation of the epithelial origin of the lesion depicted in Fig. 4 led to detailed examination of all sections, membrane by membrane, in order to follow the changes by which membranes result from degeneration of epithelial cells.

The first changes observed occur simultaneously in cytoplasm and nucleus. The cytoplasm swells slightly and becomes eosinophilic and the nucleus loses its vesicular appearance and soon becomes pyknotic (Fig. 5). Later there is an enormous increase in the size of the cell and an increase in eosinophilia. The nucleus elongates or fragments and is either passed out of the cell or blends with the cytoplasm. Finally, distinction between the cells becomes difficult except on the luminal aspect of the membrane which is somewhat irregular. This

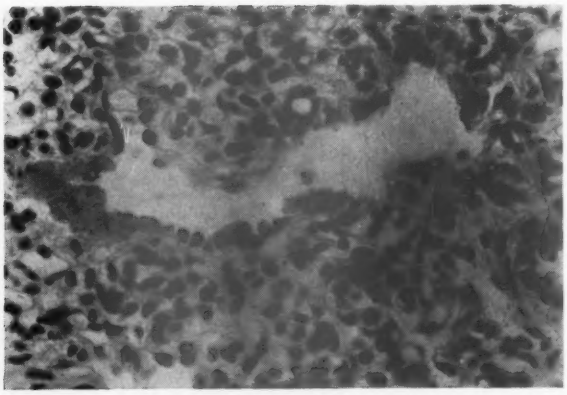


FIG. 5.—Section of respiratory bronchiole showing intact epithelial cells flanked by hyaline membrane. Some nuclei are pyknotic and others in the membrane are fragmented.
(H. and E. × 228.)

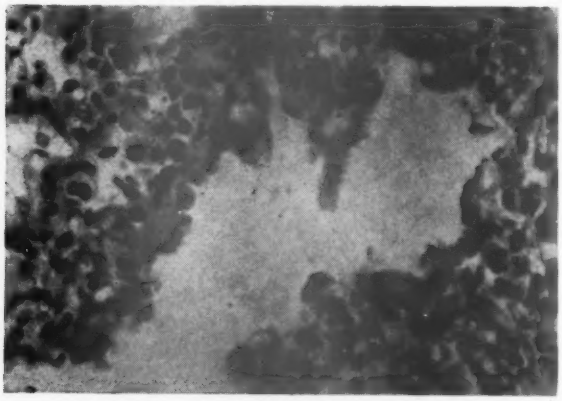


FIG. 6.—Section of respiratory bronchiole showing typical hyaline membrane and characteristic irregular edge.
(H and E. × 228.)

irregularity often accurately reflects the margins of the original cells (Fig. 6).

Clinical Features

The 133 cases resulted from 121 pregnancies. There were 67 male and 66 female infants. Nearly all died between two and 48 hours after birth (Fig. 7) and the majority died in the first 16 hours.

One hundred and twenty-three infants were premature, 10 weighed over 2,500 g. and one of these was postmature (Fig. 8). Infants below 1,000 g. showed pulmonary hyaline membranes, but the majority of the cases occurred in the 1,001-2,000 g. range.

The incidence of the lesion is inversely proportional to the gestational age and 60% were asphyxiated at birth (Fig. 9). Asphyxia is defined as taking two minutes or more to establish rhythmical respirations after delivery and most of these infants received lobeline and/or coramine. In 60% of cases it was recorded that oxygen was administered at delivery, usually by an intranasal catheter. This is a common procedure in our hospital for prematurely born infants and the actual number so treated is higher than recorded. Asphyxia at birth was more common in infants born at 34 weeks and over (76%) than in the group under 34 weeks (54%).

Of the 24 infants delivered abdominally, 20 (83%) were asphyxiated at birth and usually severely. This incidence of asphyxia is higher than for the series as a whole and suggests that it is asphyxia in cases delivered by caesarian section and not this mode of delivery *per se* which is the important factor in the subsequent development of hyaline membrane disease. In 32% of cases delivery was by breech.

The complications of pregnancy, apart from maternal diabetes, were those associated with premature delivery although the individual incidences were greater than expected in premature deliveries as a whole (Table 1). There were 24 multiple pregnancies. In 11 (10 twin, one triplet), all the infants died and showed hyaline membranes at autopsy. In 12 multiple pregnancies (11 twin, one triplet), only the second twin or third triplet was affected.

Nearly one half of the infants who died in the 1,001-2,000 g. group showed hyaline membrane formation (Table 2) but the maximum incidence occurred in the 1,001-1,500 g. group.

In 61% of the cases pulmonary hyaline membranes were the only major findings at necropsy.

The condition of the infants was poor from birth and signs of respiratory distress developed rapidly. In most infants there was no period of well-being. Lateral chest and lower sternal retraction occurred early and became progressively more severe. An expiratory grunting cry was easily heard. The four limbs often assumed an abducted and externally rotated position. Apnoeic attacks with cyanosis occurred with increasing severity. On auscultation

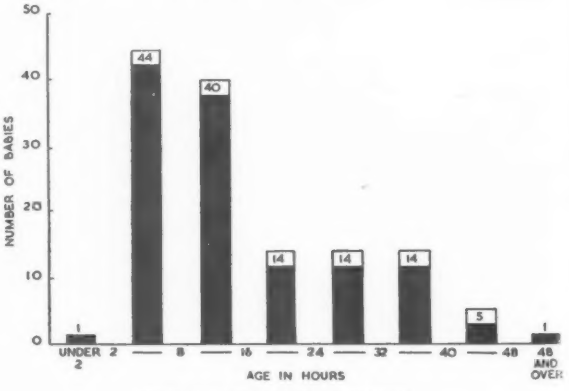


FIG. 7.—Age of infants at death.

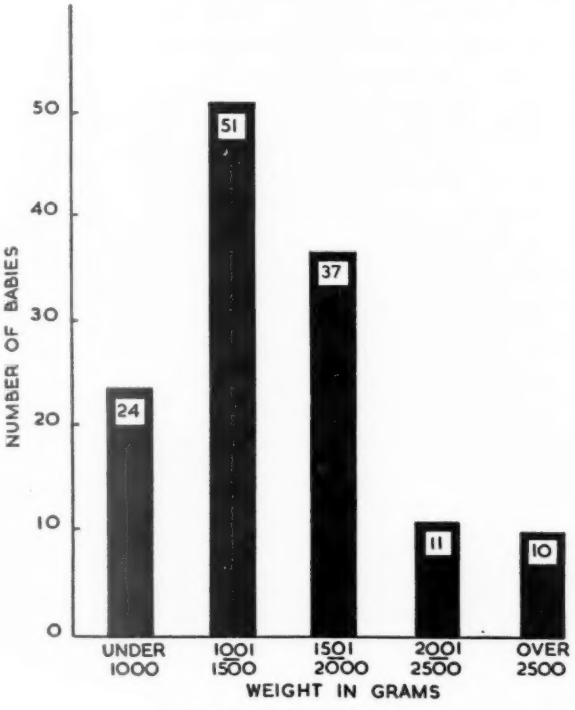


FIG. 8.—Birth weight.

the only constant finding was poor air entry into the lungs.

Discussion

The origin of hyaline membranes in infants from necrosis of epithelial cells in respiratory bronchioles has not been so described until recently (Barter, 1959). Tregillus (1951) showed lesions in the epithelial linings of terminal bronchioles but did not state clearly the relationship of such lesions to hyaline membranes; nor did he appear to appreciate that the principal lesion is confined to respiratory bronchioles. Lynch and Mellor (1955) using histochemical methods have hinted at a relationship between membranes and bronchiolar epithelial cells but so far have come to no definite conclusions about the nature of the disease. However, they have shown similar histochemical properties between epithelial cells in the respiratory tract and hyaline membranes.

Recognition of epithelial necrosis in terminal bronchioles contributed largely to our understanding of the process in respiratory bronchioles. The changes observed in an occasional terminal bronchiole are obviously those of degeneration in epithelial cells and do not occur except when hyaline membranes are present in respiratory bronchioles. The fact that nuclear material is observed in some membranes in 69% of cases led to the investigation of cases showing minimal membrane formation.

TABLE 1
COMPLICATIONS OF PREGNANCY

Multiple	24	20%
Pre-eclampsia	18	17%
Eclampsia	2	
Accidential haemorrhage	11	9%
Placenta praevia	10	8%
Diabetes	7	6%

TABLE 2
BIRTH WEIGHT, NEONATAL DEATHS AND HYALINE MEMBRANE INCIDENCE

Weight (g.)	Neonatal Deaths	Hyaline Membrane	
		Nos.	Incidence per 1,000 Live Births
Up to 1,000	184	24	125
1,001–1,500	122	51	204
1,501–2,000	71	37	78
2,001–2,500	47	11	11
Over 2,500	96	10	0·5

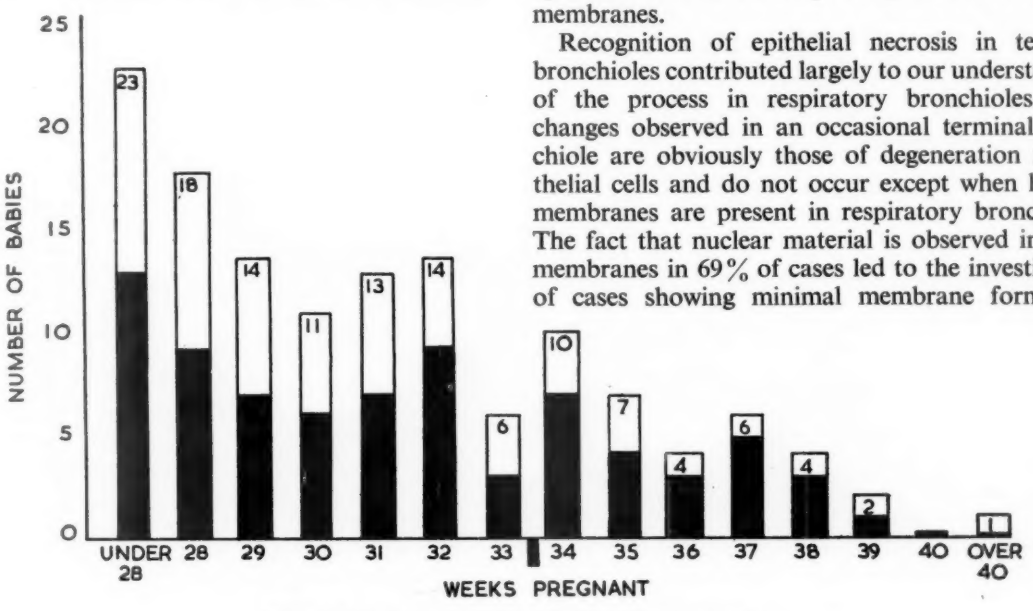


FIG. 9.—Gestational age; ▬ = number asphyxiated at birth.

All stages of epithelial necrosis from nearly intact cells to those containing faint remnants of nuclei can be observed in many of these cases. That these are the nuclear remnants of epithelial cells is evident from studying all the phases of the degenerative process. It has become clear that epithelial cell necrosis is the basis of hyaline membrane formation and that lesions are found in both terminal bronchioles and respiratory bronchioles but mainly in the latter. The epithelial linings of the trachea and bronchi are not affected and we have found no evidence that membranes form in alveolar ducts or alveoli. Furthermore, it seems likely from our own unpublished observations that alveolar tissues are not as well developed in the premature lung as commonly implied.

Much of the controversy at present about the nature of hyaline membranes centres on the assumption that the material present is derived from substances in the air spaces or from the pulmonary capillaries. Considerable evidence has been presented in favour of one or both explanations. Farber and Sweet (1931) first proposed an origin from the contents of the amniotic sac and changed the name of the lesion, hyaline membrane (Johnson and Meyer, 1925) to vernix membrane. Claireaux (1953) published the results of experimental studies in favour of an origin from aspiration of epidermal material. More recently it has been suggested that thromboplastic substances from the liquor aid in the formation of fibrin from an exudate from the capillaries (Laufe and Stevenson, 1954).

Emphasis has been placed on the exudate hypothesis by the claims of Gitlin and Craig (1956) that membranes are composed largely of fibrin. These workers used a fluorescin labelled antibody for fibrin and showed that membranes in treated sections were brightly fluorescent. Confirmation of the presence of fibrin has been afforded by van Breemen, Neustein and Bruns (1957) who studied thin sections of membranes with an electron microscope. Brown (1959) has stated that the evidence for fibrin is incontrovertible. It should be realized, however, that neither of the techniques proves that the membrane consists of nothing but fibrin. The presence of some of it is not disputed, but we believe that it results from exudation after loss of the normal epithelial lining and is only a small component of the membrane.

The reported incidence of hyaline membranes from different centres shows some variation but there is a remarkable difference between that in South India (Hadley, Gault and Graham, 1958) or Vietnam (Tran-Dinh-De, 1959) and, for example, Melbourne. Thus Hadley *et al.* found only one case in 215 neonatal deaths and from discussion with Tran-Dinh-De we estimate our incidence to be some 20 times greater than his. At present there is no explanation for these differences.

Experimental methods have not reproduced the disease in a manner corresponding to its occurrence in the human. Bruns and Shields (1954) have, however, produced what are apparently hyaline membranes in the guinea-pig lung after prolonged exposure to oxygen. These workers state that the membranes form as a result of epithelial necrosis in bronchioles. Their observations on the derivation of membranes so produced is in accord with our own in premature infants.

It is attractive to suggest that a noxious substance is the cause of the necrosis in this disease but the evidence for oxygen poisoning in the human premature infant, exposed for short periods, is incomplete.

Summary

Detailed microscopic study of the lungs of premature infants affected by hyaline membrane disease shows that the membranes result from epithelial cell necrosis in respiratory bronchioles and form *in situ*.

A description of 133 cases of hyaline membrane disease including clinical features is presented.

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PATENT DUCTUS ARTERIOSUS IN INFANCY

BY

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From the Heart Clinic, Royal Liverpool Children's Hospital

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In a report on 1,000 autopsies performed on patients dying of congenital heart disease, Abbott (1937) found that the principal lesion was a patent ductus arteriosus in 282 patients; 20% of these were infant deaths.

Subsequently numerous reports have stressed that while this abnormality can prove fatal during the first year of life, surgery in skilled hands offers an effective remedy at this age with negligible risk (Ziegler, 1952; Rudolph, Mayer, Nadas and Gross, 1958; Bauersfeld, Adkins and Kent, 1957).

Accurate diagnosis, however, may be difficult in infants. The classical continuous murmur so frequent in the older child (Hay and Ward, 1956) may not be heard, and interpretation of the signs which do present is not easy. In addition, the many complex cardiac abnormalities which are seen in infants give rise to special problems in differential diagnosis.

In this paper the clinical findings and results of ancillary investigations are analysed in 28 infants in whom patent ductus arteriosus was the sole cardiac lesion.

Clinical Findings

Symptoms and Physical Signs. The principal features of each case are set out in Table 1. Twenty-three babies presented with dyspnoea and 21 had had bronchitis. Recurrent respiratory infections often severe and accompanied by marked breathlessness caused concern in 13 babies (46%); dyspnoea, accentuated by feeding or crying, was common in this group and all 13 were under weight when first seen.

Heart failure as evidenced by peripheral oedema, hepatomegaly and lung crepitations occurred in four cases (Cases 1, 2, 11 and 14); in three it was precipitated by bronchopneumonia.

The 'waterhammer' character of the pulse was noted in all cases and often provided the first clue to the diagnosis. It was not always easily detected at the wrist, particularly in the restless infant, but was always readily felt in the tibial vessels at the ankle. In 17 infants (60%) the waterhammer quality was very impressive.

A systolic thrill was noted in 12 cases (43%) and this was usually localized to the pulmonary area. A murmur which began after the first sound and which extended through the second sound into diastole was audible in 22 babies (78%). The classical 'machinery' quality was rare, though a low-pitched systolic rattle was often heard. The murmur extended into diastole for a variable period but was seldom as long as the typical murmur in older children. We have, nevertheless, defined this murmur as being continuous because it continues through the second sound from systole into diastole as Gibson (1900) originally defined it. The continuous murmur was confined to the second left intercostal space, but the systolic element was widely conducted and sometimes even louder in the third or fourth left intercostal spaces close to the sternal edge. In the remaining six cases a continuous murmur was not present and the point of maximal intensity of the systolic murmur was difficult to determine. An independent apical mid-diastolic murmur was recorded in 18 infants (64%). Four of these had no continuous murmur and the diastolic murmur was the most striking one; catheterization was done in three of these four cases and all three had marked pulmonary hypertension.

Radiography. Standard antero-posterior and oblique films were taken in all cases. Pulmonary plethora associated with some degree of cardiac enlargement was present in all. The cardiac contour was not in any way characteristic, though 14 infants (50%) showed a well-defined pulmonary arc. Selective enlargement of the left ventricle was suggested in 18 (64%), and of the left atrium in seven (25%).

Electrocardiography. Standard and unipolar limb leads as well as four praecordial leads (V3R, V1, V3 and V6) were recorded in all cases. Interpretation was based on Ziegler's (1951) criteria.

Case No.	Age	Symptoms			Signs				Radiograph	
		Dyspnoea	Bronchitis	Heart Failure	Thrill	C.M.	M.D.M.	B.P.	C.T. ratio	L.A.
1	12 days	++	++	+	+	0	+	95 syst.	0·7	N
2	24 days	+	+	+	0	+	+	100/0	0·68	+
3	7 weeks	++	++	0	+	+	+	100/0	0·66	N
4	8 weeks	++	+	0	0	+	+	110/40	0·6	N
5	3 mths	++	+	0	0	+	0	85 syst.	0·67	+
6	4 mths	++	++	0	0	0	+	75 syst.	0·63	N
7	4 mths	+	+	0	0	+	+	120/55	0·65	+
8	5 mths	++	0	0	+	+	+	105/0	0·67	+
9	5 mths	++	+	0	0	+	0	not recorded	0·6	N
10	5 mths	++	+	0	0	+	0	80/0	0·56	N
11	5 mths	++	0	+	0	+	+	120/70	0·67	N
12	5 mths	+	+	0	+	0	0	not recorded	0·6	N
13	5 mths	+	0	0	0	+	0	115/75	0·62	N
14	5 mths	++	++	+	0	0	+	not recorded	0·63	N
15	6 mths	++	++	0	0	0	0	110/70	0·58	N
16	6 mths	0	+	0	+	+	+	95 syst.	0·59	+
17	6 mths	++	++	0	+	0	+	95/10	0·61	N
18	6 mths	0	+	0	+	+	+	120/60	0·62	N
19	7 mths	++	0	0	+	+	+	110/60	0·7	N
20	8 mths	+	++	0	0	+	0	not recorded	0·6	N
21	9 mths	0	++	0	0	+	0	100/0	0·6	N
22	9 mths	+	0	0	0	+	+	120/70	0·8	+
23	9 mths	+	+	0	0	+	+	100/0	0·64	+
24	10 mths	+	0	0	0	+	0	100/0	0·6	N
25	10 mths	++	++	0	+	+	+	115/55	0·64	N
26	11 mths	+	+	0	+	+	0	120/70	0·59	N
27	11 mths	0	++	0	+	+	+	95/45	0·58	N
28	12 mths	0	0	0	+	+	+	not recorded	0·57	N

Notes: C.M. = Continuous murmur. M.D.M. = Mid-diastolic murmur. B.P. = Blood pressure.

Vertical or semi-vertical electrical position was usual: only one horizontal heart was found. The electrical axis was normal in 23 (82%), four showed right axis deviation and one left axis deviation. There was evidence of left atrial enlargement in four patients. In 13 (46%) ventricular activity was normal. Left ventricular hypertrophy was evident in 11 records (40%), always with an isoelectric S.T. segment and a normal upright T wave in the left ventricular leads. Combined right and left ventricular hypertrophy was recorded in four cases (14%) while isolated right ventricular hypertrophy was present in only one (Case 19).

A pattern consisting of large RS deflections over the right ventricle with normal activity in left ventricular leads and deep Q waves in leads III and aVF was recorded in eight cases (28%). In all of these the duct measured 7 mm. or more (Cases 1, 6, 8, 11, 12, 15, 22 and 28) and in three there was marked pulmonary hypertension (Cases 1, 6 and 15).

The prevalence of deep Q waves in this series was an interesting feature. They were invariably present in lead V6, measuring 3 mm. or more in 12 instances (43%). Twenty-three infants (80%) showed a deflection of 3 mm. or more in either lead

Electrocardiogram										Age at Operation (mths)	Diameter of P.D.A. (mm.)
III	aVF		V3R		V1		V6				
R	Q	R	R	S	R	S	Q	R	S		
9	2·5	5	15	16	15	16	1	4	11	24	14 divided
14	2	12	4	2	12	8	1	14	10	2	6
1	1	3	20	27	24	25	3	11	0	3	5
12	3	11	7	2	8	1	3	19	0	9	6
9	2	13	8	7	8	8	1	15	0	4	5
13	5	10	18	22	18	24	1	13	0	13	7
10	0·4	15	7	15	14	28	2	23	0	5	7
13	4	15	11	11	15	14	2	15	0	5½	7
10	3	6	14	0	5	0	1	13	0	Died at 6½ mths; autopsy	5
20	4	15	14	0	12	8	1	15	1	9	6
16	17	9	20	22	15	22	2	14	0	5	9 divided
6	8	12	24	34	23	34	4	5	0	Died at 11 mths; autopsy	7
11	2	10	8	13	8	20	10	34	0	7 yrs.	7
12	6	11	18	3	14	5	1	8	7	Died at 12 mths; autopsy	15
14	9	10	24	23	23	24	8	8	0	14	14
17	10	15	14	14	13	19	1	23	0	27	7
15	4	15	1	13	1	13	2	23	—	9	10
5	1	9	10	10	18	19	1	11	—	12	6·5
2·7	0	4	13	1	26	0·2	1	7	13	Died at 7 mths; no autopsy	—
14	2	12	5	6	3	5	2	14	0	12	6
14	3·5	15	5·5	9	5	10	3	17	0	13	6·5
12	4	12	12	11	12	15	6	16	0	9	9
40	14	26	8	12	9	12	8	35	0	11	6
11	1	12	9	8	7	9	3	23	0	4½ years	10
7	2	11	10	13	9	9	5	29	0	14	5
12	3	14	11	16	8	20	5	20	0	11	6
10	5	10	6	8	5	10	1	12	0	13	7
12	5	9	10	7	8	8	4	13	0	12	7

. ratio = Cardio-thoracic ratio. L.A. = Left atrium. L.V. = Left ventricle. P.D.A. = Patent ductus arteriosus.

111 or aVF. The amplitude of the QRS complexes in leads 111, aVF, V3R, V1 and V6 are tabulated (Table 1).

Special Investigations. Cardiac catheterization was performed in four of the 28 infants (Cases 1, 6, 15 and 17) in whom the diagnosis remained uncertain after clinical, electrocardiographic and radiographic examination (Table 2). All had marked pulmonary hypertension and in three (Cases 1, 6 and 15) the greatest difference between the pulmonary artery and aortic pressures during sedation was 4 mm. Hg. In one of these there was evidence of a left to right shunt through the ductus but in the other two the diagnosis was confirmed by passing the catheter into the descending aorta.

Venous angiocardiography was carried out in one (Case 3) when the catheter could not be advanced into the pulmonary artery. This showed dilatation of the left pulmonary artery with dilution of the contrast medium in the artery at the site of entry of the patent ductus.

Treatment

When heart failure was present it was treated with digoxin and diuretics. Pulmonary infections

TABLE 2

CARDIAC CATHETERIZATION

Cases	Oxygen Saturation (%)			Pressures in mm. Hg		Diameter of Ductus (mm.)	Fall in Pressure in Pulmonary Artery after Clamping Ductus (mm. Hg)
	S.V.C.	P.A.T.	Aorta	P.A.T.	Aorta		
1 (R.D.)	63	63	80	94/62	98/60	14	34
6 (I.W.)	46	54	59	88/58	92/58	7	10
15 (S.B.)	58	58	69	132/80	130/70	14	14
17 (R.W.)	50	84	not entered	84/44	not entered	10	not measured

S.V.C. = Superior vena cava P.A.T. = Pulmonary artery trunk

were treated with antibiotics. All the patients responded satisfactorily to treatment and operation was never performed in the presence of heart failure or infection.

The ductus was either ligated or divided, depending on its size, in 24 of the 28 infants. There were no deaths and closure was incomplete in only one infant in whom the duct was found to be broad and frail. The age at operation and minimum external diameter of the ductus is tabulated (Table 1).

The remaining four infants (Cases 9, 12, 14 and 19) died while awaiting admission for further assessment and operation. Two of these had other serious abnormalities (one, Case 14, had Albers-Schönberg's disease, and the other, Case 9, had Möbius' syndrome); one, Case 19, developed fulminating gastroenteritis, and the fourth baby, Case 12, developed bronchopneumonia at home and died.

Differential Diagnosis

In the majority of infants patency of the ductus may be differentiated from other lesions with confidence after clinical examination, radiography, electrocardiography and phonocardiography. In some babies, on the other hand, a large patent ductus may present without any of the typical signs and differential diagnosis is difficult. The lesions with which patent ductus arteriosus is most commonly confused in the early months of life are persistent truncus arteriosus and ventricular septal defect. Another important consideration is that a patent ductus may be compensating for a more serious underlying lesion and this possibility must always be borne in mind.

The following case summaries are detailed to illustrate the problems involved in the diagnosis of patent ductus arteriosus. The first two cases (Case 2 and Case 1) show that the clinical picture of a small ductus without pulmonary hypertension differs widely from that of a large ductus with pulmonary hypertension at systemic level. The third case shows how even when the ductus is compensatory it may dominate the clinical picture.

The fourth case shows how closely persistent truncus arteriosus may resemble patent ductus arteriosus in the first few months of life.

B.L. Case 2. Small patent ductus. Normal delivery followed an uncomplicated pregnancy. The birth weight was 7 lb. 4 oz. Bronchopneumonia at 2 weeks of age led to admission to hospital, where heart failure was diagnosed in addition to pneumonia. Improvement followed therapy with penicillin and digoxin. He was transferred to this clinic when 3½ weeks old. At that time he weighed 5 lb., was poorly nourished and had slight dyspnoea at rest. There was a waterhammer arterial pulse and a continuous murmur in the pulmonary area with an independent apical mid-diastolic murmur. Phonocardiography showed that the murmur began after the first sound, reached a late systolic crescendo and extended without interruption into early diastole (Fig. 1). Both aortic and pulmonary valve closure were clearly recorded in the second left intercostal space. The heart was enlarged radiologically (C.T. ratio 0·68) with selective enlargement of the left atrium and there was pulmonary hyperaemia. The electrocardiogram was normal.

At thoracotomy a patent ductus arteriosus of minimal external diameter 6 mm. was transfixed and ligated. Progress since then has been entirely satisfactory. The child is gaining weight well and has no dyspnoea. His heart sounds are normal and there are no murmurs.

COMMENT. In this case the clinical, radiographic, electrocardiographic and phonocardiographic appearances were typical of a patent ductus which was confirmed at thoracotomy.

R.D. Case 1. Large patent ductus arteriosus with marked pulmonary hypertension. This male infant was born by normal delivery after eight months of uncomplicated pregnancy and weighed 5 lb. 13 oz. at birth. Normal respirations developed spontaneously and his general condition seemed satisfactory. Heart failure developed on the third day of life and a loud systolic murmur was noted.

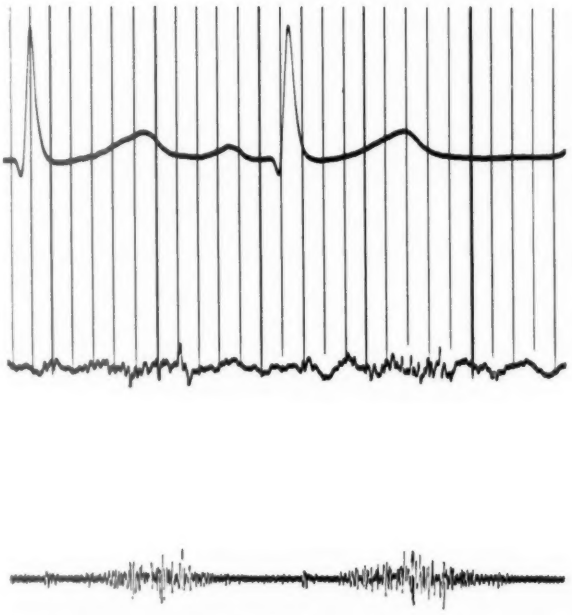

FIG. 1.—Phonocardiogram recorded from second left interspace showing continuous murmur with late systolic accentuation.

When first seen at this clinic on the 12th day of life, his condition had improved following digoxin therapy though dyspnoea and moderate oedema of the extremities persisted, and some fine crepitations were noted at the base of the right lung. The arterial pulses were regular and of 'full' volume. A long systolic murmur of low-pitched blowing quality was heard in the pulmonary area and down the left sternal edge, the point of maximum intensity being uncertain. No diastolic murmur was heard.

Radiography showed marked generalized cardiac enlargement and increased pulmonary vascularity.

Electrocardiography showed right axis deviation, a vertical heart and large R/S deflections over the right ventricle (R V3R 15 mm., S V3R 16 mm.). In the left ventricular leads tall T waves suggested left ventricular diastolic overload, though the height of the R waves were within normal limits (R V6 4 mm.). A provisional diagnosis of ventricular septal defect was made.

PROGRESS. The signs of congestive failure gradually disappeared with continued digoxin therapy. Dyspnoea persisted and at 6 weeks the infant weighed only 5 lb. 10 oz. He was seen regularly in the clinic and his progress over the next two years was punctuated by monthly attacks of bronchitis, occasional cyanotic episodes, usually associated with feeding difficulties, and persistent moderate dyspnoea at rest. He gained weight slowly and was only 23 lb. at 2 years. He did not stand with support until he was 2 years old and had not begun to walk at that age. The clinical signs in the cardiovascular system varied little throughout this period. The arterial pulses were always of full volume and a waterhammer quality was occasionally recorded. The systolic murmur persisted and latterly was accompanied by a faint systolic thrill in the second and third left intercostal spaces. The second sound in the pulmonary area was accentuated and finely split.

Cardiac enlargement was a constant radiological finding but became relatively less marked with age. The pulmonary arc became more clearly defined after the second month. A moderate degree of pulmonary plethora persisted.

In the electrocardiogram the pattern of the precordial leads varied little; the amplitude of the individual deflections showed occasional fluctuations, but these were never constant in any one direction. At the age of 2 years left ventricular overactivity was still indicated by large S waves in the right ventricular leads (S V1 25 mm.). By this time right ventricular hypertrophy was also suggested (R V1 20 mm.), and impressive Q waves had developed in standard lead 111 and unipolar limb lead aVF. These Q waves first appeared when the child was 3 months old and gradually became deeper.

The diagnosis was established when the child was 2 years old by cardiac catheterization, the descending aorta being easily entered through a large patent ductus. There was little change in pressure when the catheter was withdrawn from the aorta to the pulmonary artery and oxygen saturation figures failed to show a left to right shunt at pulmonary artery level when the child

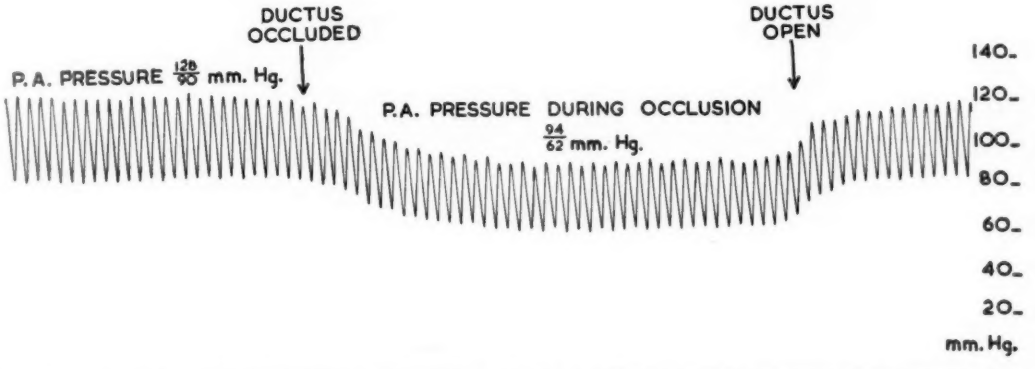

FIG. 2.—Pressure tracing from pulmonary artery at thoracotomy in Case 1, showing fall in pulmonary artery pressure after occlusion of the ductus.

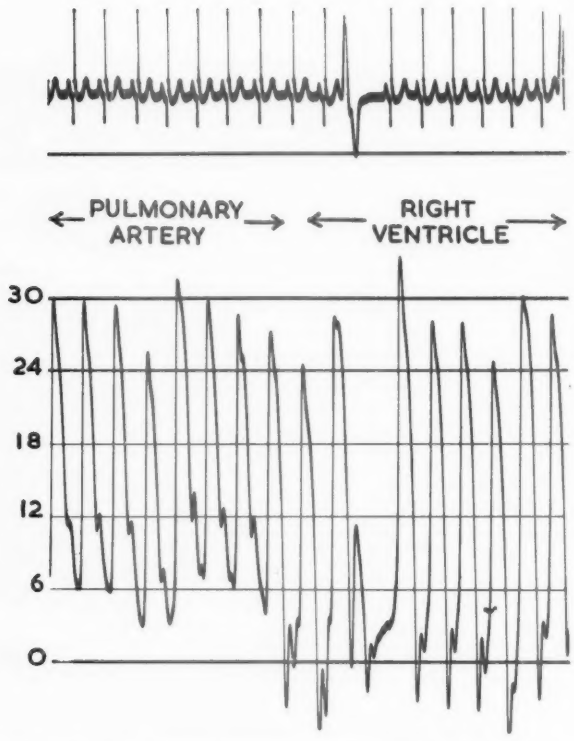

FIG. 3.—Pressure tracing showing normal pressures in pulmonary artery and right ventricle in Case 1, 13 months after operation.

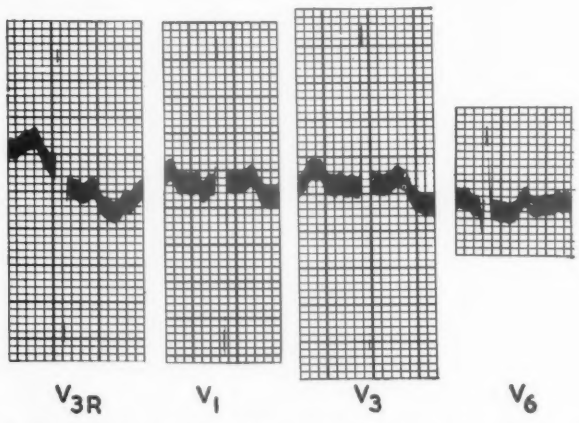

FIG. 4.—Electrocardiogram showing increased R and S waves in V3R and V1 with a normal R wave in V6, a pattern commonly seen in large patent ducts with marked pulmonary hypertension.

was sedated at catheterization (Table 2). Thoracotomy was recommended and a 14-mm. ductus was found. The pressure in the pulmonary artery fell markedly after clamping of the duct (Fig. 2) which was then divided.

The child's general condition rapidly improved following operation and breathlessness became less marked. His subsequent progress has been excellent with marked increase in activity; he has gained weight more quickly and has been completely free from attacks of bronchitis.

Recatheterization performed 13 months after operation showed a normal right ventricular and pulmonary artery pressure (Fig. 3). Chest radiographs show some pulmonary hyperaemia but the heart size is now normal. The electrocardiogram has also reverted to normal though prominent Q waves persist in leads 11, 111, and aVF.

COMMENT. This case illustrates how a large patent ductus arteriosus with pulmonary hypertension at systemic level may be mistaken for a more serious lesion. This led to delay in carrying out special investigations which enabled the diagnosis to be made.

Three other infants in this series (Cases 6, 14 and 15) presented similar features and catheterization established the diagnosis in two (Cases 6 and 15, Table 2). All three were dyspnoeic, under weight and suffered from recurrent pulmonary infections. All had 'waterhammer' pulses of a variable degree and two had apical mid-diastolic murmurs. All showed similar electrocardiographic records (Fig. 4), and all had some cardiac enlargement and pulmonary plethora. In these three babies the clinical signs were inconclusive and the results of routine investigations equivocal. It seems that all such obscure cases should be catheterized at an early age if surgical treatment is to be performed while the pulmonary hypertension is still completely reversible.

D.G. Compensatory Patent Ductus Arteriosus. This infant was the first of binovular twins born by breech delivery at full term. She then weighed 4 lb. 12 oz. Late pregnancy had been complicated by moderate toxaemia. There was a history of breathlessness since birth, but cyanosis had not been noticed. Pulmonary infection occurred during the third week of life and cardiac failure developed.

On admission to this clinic at 3 weeks of age the infant was pink and breathless with oedema of feet, arms and eyelids. The arterial pulse was waterhammer in character and a long systolic thrill was present in the pulmonary area. There was a long rattling systolic murmur extending into early diastole in the pulmonary area and an independent mid-diastolic murmur at the apex.

Radiography showed marked cardiac enlargement (C.T. 0·72) and moderate pulmonary hyperaemia (Fig. 5).

Electrocardiography showed right atrial enlargement (P2 = 3 mm. peaked) with low voltage complexes in V3R and V1 and left ventricular hypertrophy with depression of the S-T. segments and inverted T waves in V5 and V6.

Treatment with digoxin and diuretics was followed by some improvement, but feeding remained difficult and she did not gain weight. Heart failure persisted despite treatment. Thoracotomy was therefore recommended when she was 6 weeks of age and a 6 mm. patent ductus was ligated. Following operation the infant's condition deteriorated still further and she died 12 hours later. Autopsy showed tricuspid atresia.

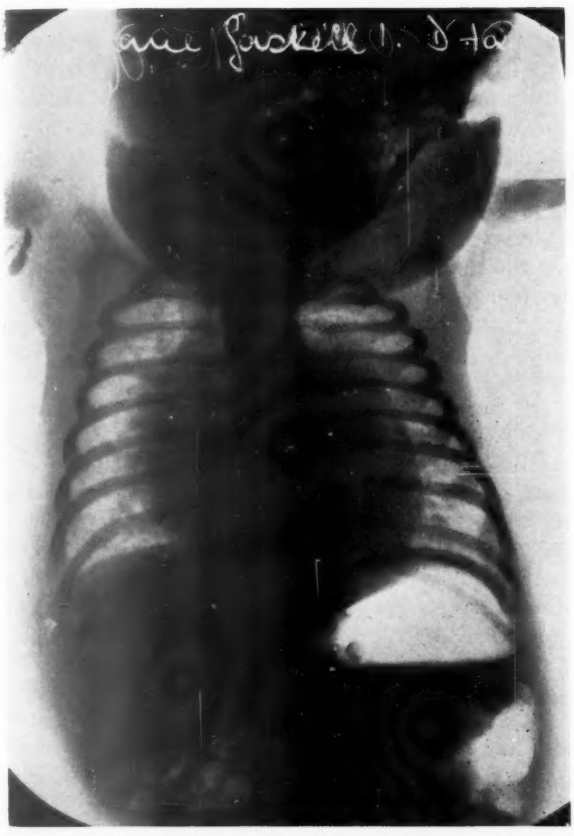

FIG. 5.—Radiograph showing plethoric lung fields in case of tricuspid atresia with overcompensating patent ductus arteriosus.

COMMENT. This case illustrates the extent to which a patent ductus arteriosus may completely dominate the clinical picture even though it is compensating for a lesion which causes pulmonary oligaemia.

Our experience of such dominance is, however, limited to tricuspid atresia, for all our babies with Fallot's tetralogy and pulmonary atresia with a patent ductus, have shown not only central cyanosis, but also normal or diminished pulmonary vascularity.

The fact that heart failure did not respond to medical treatment in this infant and the presence of left ventricular strain in the electrocardiogram should have made the diagnosis of a simple patent ductus arteriosus suspect. In a subsequent similar case attention to these findings enabled us to diagnose the same combination of defects, which were subsequently proved at autopsy.

D.E. Case of Persistent Truncus Arteriosus. This premature infant was born by normal delivery after eight months uncomplicated pregnancy. Initial progress was satisfactory, but increasing breathlessness was noted from the 5th week. On admission to this clinic when 11 weeks old she was pink and moderately dyspnoeic at rest. The waterhammer quality of the arterial pulse was striking. Blood pressure was 120/0 mm. Hg. A continuous murmur was heard in the pulmonary area and there was an apical mid-diastolic murmur. Phonocardiography confirmed these findings, but the second sound was not seen owing to the high amplitude of the murmur.

Radiologically the heart was enlarged (C.T. ratio 0·75) the oblique views showed selective left ventricular enlargement, and there was increase in the pulmonary vascularity.

The electrocardiogram showed left ventricular hypertrophy with 1 mm. S-T depression and T wave inversion in leads V5 and V6. Right ventricular activity was within normal limits.

The diagnosis of patent ductus arteriosus was made and thoracotomy recommended. At operation, however, a persistent truncus arteriosus was found. The infant's condition deteriorated rapidly during exploration of the chest; ventricular fibrillation developed and she died.

COMMENT. In this case clinical examination suggested a patent ductus arteriosus. The picture was, however, incomplete because splitting of the second sound in the pulmonary area was neither audible nor clearly seen on the phonocardiogram and left ventricular systolic overload in the electrocardiogram was an unusual finding in patent ductus arteriosus in infancy.

This infant is one of a group of 10 cases of persistent truncus arteriosus seen at this clinic. Although cyanosis was prominent in half of these babies the other five were pink when first seen and presented many of the typical features of patent ductus arteriosus. The five acyanotic infants had markedly collapsing pulses and two of them had continuous basal murmurs with independent apical mid-diastolic murmurs. Radiographic and electrocardiographic appearances were similar to those seen in patent ductus arteriosus. These acyanotic infants had severe symptoms and after observation for a few weeks slight cyanosis with feeding became evident and led to further investigation in all except the case described. In two cases, cardiac catheterization demonstrated a left-to-right shunt at pulmonary artery level, but venous angiocardiography failed to reveal the common truncus and patent ductus arteriosus was wrongly diagnosed; both these patients died at thoracotomy. In the other two cases selective angiocardiography with injection of dye into the right ventricle outlined the common trunk and thoracotomy was avoided.

Slight cyanosis after crying or feeding is an extremely important feature in these cases. Angiocardiography is required to make the diagnosis, for cardiac catheterization alone may fail to indicate the ventricular septal defect which is always present with persistent truncus arteriosus, and the increased oxygen level in the blood in the common trunk suggests patent ductus arteriosus. If the right ventricular pressure is at systemic level and the catheter is not passed through a ductus into the descending aorta persistent truncus arteriosus should be suspected and selective angiocardiography should be performed.

Signs of left ventricular systolic overload in the electro-

cardiogram occurred in three cases of truncus arteriosus, but none of the patent ducts, so this should always suggest the possibility of truncus arteriosus. If phonocardiography shows two sounds due to the independent closure of the aortic and pulmonary valves, persistent truncus arteriosus is eliminated.

DISCUSSION

Diagnosis

Clinical Signs. Most authors have emphasized the value of the bounding or brisk peripheral pulses and wide pulse pressure in the diagnosis of patent ductus arteriosus, though varying emphasis is based on their importance. This characteristic pulse persists even during tachycardia or heart failure, as long as the dominant shunt is from aorta to pulmonary artery (Ziegler, 1952). When, however, complete reversal of flow through the ductus occurs the pulses are of normal or small volume (Anderson, Adams and Varco, 1956). Complete reversal of flow is rare in infancy so the waterhammer pulse frequently provides an early clue to diagnosis. It was present in all our cases and we agree with Reinhold (1958) that it is the most important diagnostic sign. There is usually a wide pulse pressure, the aortic diastolic pressure being low; nevertheless, waterhammer pulses were also prominent in those infants with marked pulmonary hypertension; this is probably because the ductus in such cases is a large one and a significant left-to-right shunt still occurs even though the pulmonary artery pressure is very close to the systemic pressure. Indeed, in the presence of marked pulmonary hypertension a waterhammer pulse may be the only clinical sign which suggests a diagnosis of patent ductus arteriosus.

Waterhammer pulses may occur in conditions other than a patent ductus arteriosus, but the most marked examples of such pulsation were observed in acyanotic infants with persistent truncus arteriosus.

The proportion of cases with a continuous murmur varies considerably in published reports of series of patent ductus arteriosus. This may be due in part to the varying number of infants with marked pulmonary hypertension in each series. In addition, the interpretation of the term 'continuous murmur' varies; it is used in this clinic when the murmur continues through the second sound into diastole regardless of its duration in diastole. In our series all cases uncomplicated by marked pulmonary hypertension did have a continuous murmur when first seen, the youngest being 24 days old (Case 2). The typical machinery qualities of the murmur were uncommon, but a characteristic systolic rattle or crackle as described by Keith, Rowe and Vlad (1958) was often heard.

A mid-diastolic murmur, attributed to increased flow through the normal mitral valve, was a common finding and gave rise to triple rhythm at the apex. Since in some infants this may be the most striking praecordial murmur, even in the presence of marked pulmonary hypertension, its presence should always suggest the possibility of patent ductus arteriosus. An identical murmur, however, may occur in association with ventricular septal defect, persistent truncus arteriosus, aorto-pulmonary window and congenital mitral stenosis.

Of particular interest are the three patients (Cases 1, 6 and 15) in whom the pulmonary artery and aortic pressures were so close. All these patients showed a fall in pulmonary artery pressure when the ductus was clamped at operation and all have done extremely well since operation. In the one which has been recatheterized, the right ventricular and pulmonary artery pressures are normal and there is no evidence of a shunt. This illustrates that despite almost balanced pressures in the pulmonary artery and aorta, the pulmonary artery pressure could revert to normal after treatment and that the factors contributing to the marked hypertension were completely reversible. We do not know when irreversible changes may develop in such a case, but it seems that the earlier the diagnosis is established and treatment carried out the more likely is a complete cure. We stress then the importance of finding a collapsing pulse in an acyanotic patient who may or may not have an apical diastolic murmur, who has plethoric lung fields on the radiograph and electrocardiogram changes described in Case 1. Catheterization should be carried out in the hope of finding a patent ductus arteriosus.

Phonocardiography. Experience with recent cases in this clinic has confirmed the findings of Reinhold and Nadas (1954) in the older child and convinced us of the value of phonocardiography. The graphic record illustrates the onset of the murmur after the first sound and its late systolic accentuation, and confirms its uninterrupted extension into diastole (Fig. 6). Though the loud murmur may mask the second heart sound at the base of the heart, exploration of the whole precordium is worth while as the separate closure of the aortic and pulmonary valves can often be recorded from the lower sternal edge (Fig. 6). The demonstration of these two independent sounds is important in the exclusion of a persistent truncus arteriosus.

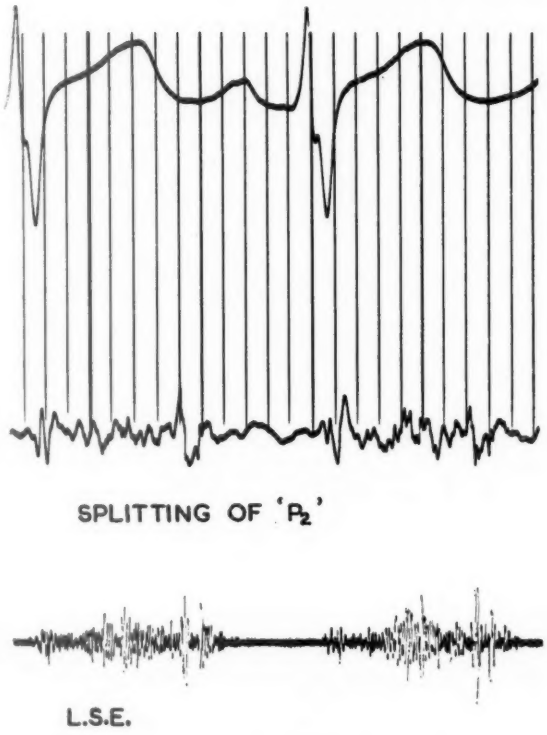

FIG. 6.—Phonocardiogram showing continuous murmur. The two components of the second heart sound were best recorded at the left sternal edge.

Radiography. Some cardiac enlargement and pulmonary plethora is invariable and left ventricular or left atrial enlargement common. The pulmonary arc is often prominent after the early months of life and both this vessel and the aortic knuckle pulsate vigorously on screening. These appearances, though frequent in patent ductus arteriosus, are also found in other lesions, particularly ventricular septal defects.

Electrocardiography. The electrocardiogram may be within normal limits even though the child has symptoms and there is convincing clinical and radiological evidence of a left-to-right shunt (Cases 1, 8 and 22) or marked pulmonary hypertension (Dammann and Sell, 1952). In most cases, however, the electrocardiogram is abnormal. In this series, evidence of isolated left ventricular hypertrophy was the commonest finding. Isoelectric S-T segment and upright T waves of normal or increased amplitude were always present in the left ventricular leads. In contrast, T wave inversion with or without S-T depression appeared in two cases of persistent truncus arteriosus and in both patients in whom tricuspid atresia accompanied patency of the ductus. Though left ventricular strain may occur in older children with large uncomplicated patent ducts (Cosh, 1957; Hay and Ward, 1956), when it is thought to be due to coronary insufficiency, its presence in infancy makes us suspect some other lesion.

Isolated right ventricular hypertrophy was seen in only one case (Case 19). Clinical examination of this patient did not suggest either the presence of marked pulmonary hypertension or an associated pulmonary stenosis. Unfortunately the child died from fulminating gastroenteritis and autopsy was not allowed. Bauersfeld *et al.* (1957) have, however, reported the presence of isolated right ventricular hypertrophy in patent ductus arteriosus without pulmonary hypertension or pulmonary stenosis being present.

Rudolph *et al.* (1958) stated that combined ventricular hypertrophy frequently occurs in infants with patent ductus arteriosus and this was present in four of our cases (Cases 1, 3, 12 and 15). In these records, left ventricular hypertrophy was diagnosed because of the deep S waves in V3R and V1; the R wave in V6 was not increased in amplitude. The three infants who were proved at cardiac catheterization to have marked pulmonary hypertension showed this pattern on the electrocardiogram and in all three the Q waves were deep in leads 111 and aVF. Unfortunately, all the large ducts have not shown these features and identical records have been found in ventricular septal defects. Nevertheless, when these electrocardiographic changes occur in an infant the possibility of patent ductus arteriosus should be considered.

Deep Q waves are a common feature in infant records in leads 111 and aVF occurring in 40% of normal infants. Nevertheless, deep Q waves occurred in 80% of the infants who had patent ductus arteriosus and their presence may be of help in differential diagnosis as they are in the adult patient with a patent ductus arteriosus accompanied by marked pulmonary hypertension (Wood, 1958).

Right bundle branch block patterns have been reported in infants with patent ductus arteriosus (Ziegler, 1952; Nadas, 1957), but did not occur in our series.

Cardiac Catheterization. This procedure is as safe in infancy as in older patients. Over 50 infants have been catheterized in this clinic without any complication.

Catheterization was done only when the diagnosis could not be established after clinical, radiographic and electrocardiographic examination. In such cases the pulmonary artery pressure is usually at or

near systemic level. The diagnosis of patent ductus arteriosus is often established by passing the catheter through the ductus, which is usually large in such cases, and the presence of a left to right shunt and any right to left shunt can be confirmed by blood oxygen estimations. If, however, the pulmonary artery pressure is at systemic level and the catheter cannot be passed through a ductus or enters a branch of the aorta, usually the right subclavian artery, then further investigation by angiography or aortography is required to differentiate the lesion from patent ductus arteriosus, aortopulmonary window or a high ventricular septal defect in which there was no rise in oxygen saturation at ventricular level.

Angiography. Venous angiocardiography will demonstrate dilution of dye in the pulmonary artery when a patent ductus arteriosus or aortopulmonary window is present if there is a left to right shunt. It may, however, fail to outline a common truncus adequately and has largely been replaced in this unit by selective angiocardiography.

Aortography. Injection into the brachial artery may show a shunt from aorta to pulmonary artery but fail to outline a common truncus. Retrograde aortography when the dye is injected through a catheter with the tip lying above the aortic valves is probably the best way of differentiating the various lesions when the right ventricular pressure is at systemic level. This investigation has a 4% mortality (Bauersfeld *et al.*, 1957) and has not been used in this clinic.

Treatment

It is generally accepted that patent ductus arteriosus should be treated surgically. If symptoms are severe early operation is essential. In the absence of symptoms, Carter and Waterston (1951) advise operation shortly before children start school. We favour earlier surgery when the diagnosis is established in infancy and have advised operation in this age group even though the infants have few symptoms. Spontaneous closure of the ductus is rare, recurrent bronchitis is common, and growth and physical development are often retarded. Infants tolerate operation very well and seem less disturbed by admission to hospital than toddlers and young children.

When the ducts are small they are doubly ligated and in addition transfixed; when large (over 10 mm.) they are divided.

It is important that operation should not be undertaken during a respiratory infection or in the presence of heart failure. Even when the ductus is large the patient responds to treatment with digoxin and diuretics, and it is our experience that if congestive cardiac failure persists after medical treatment there is some other lesion present.

SUMMARY

The findings in 28 infants in whom a patent ductus arteriosus was the sole cardiac abnormality are reviewed in an attempt to define the clinical features in infancy and to assess the value of routine radiography and electrocardiography.

The different clinical findings in small and large patent ducts are illustrated and the similarity of this lesion to some cases of persistent truncus arteriosus in the early months of life is described. The pitfalls caused by an overcompensating ductus are discussed.

The indications for cardiac catheterization and angiocardiography and their value in differential diagnosis are also considered. The problems of surgical treatment are mentioned.

We are indebted to Professor J. D. Hay for his advice and criticism of this paper, to Mr. F. R. Edwards and Mr. B. J. Bickford who operated on these cases, and to anaesthetists, Dr. G. J. Rees and Dr. A. Stead. We are also grateful to Dr. Norah Walker and Dr. C. M. Davies for their help in interpretation of the radiographs and angiocardiograms.

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CONGENITAL ADENOMATOID MALFORMATION OF LUNG WITH PNEUMOTHORAX

BY

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Although hamartomas of the lungs are not common, they cannot be considered as pathological curiosities. Several cases have been reported in recent years (Harris and Schattenberg, 1942; Jones, 1949; Thomas, 1949; Timossi, 1955; Lima, Zerbini and Bittencourt, 1955; Gottschalk and Abramson, 1957; Galvez Fermin, 1958; Cornéa, Dichter, Gamentay and Mindru, 1959; Bain, 1959). One variety of hamartoma of the lung, namely congenital cystic disease of the lung, has received an increasing amount of attention since Koontz (1925) collected his large series of cases. Ch'in and Tang (1949) coined the expression 'congenital adenomatoid malformation' for this condition. They found descriptions of 10 cases in the literature up to that time and added one case of their own.

A comprehensive review of the literature was made by Craig, Kirkpatrick and Neuhauser (1956). They mentioned the 11 cases in Ch'in and Tang's paper, 11 other cases and added four of their own. Coffee (1956) also reviewed the position at that time. Since then, one case by Goodyear and Shillitoe (1959) and four cases by Herrmann, Jewett and Galletti (1959) have been reported. These workers distinguished between those cases which present clinically in early neonatal life with cyanosis and those which present later with signs of infection. This report is concerned with a case of congenital cystic disease of the lung which was accompanied by hypoplasia of the entire remaining lung tissue and in which a tension pneumothorax occurred following attempts at resuscitation.

Case Report

Clinical History. The mother was 26 years of age and had had one previous normal pregnancy. Her general health was good. During pregnancy the only abnormality detected was hydramnios at about 27 weeks.

The onset of labour was spontaneous and occurred at the end of the 28th week. The duration of the first stage was one hour and of the second stage 20 minutes. The presentation was vertex and delivery was spontaneous.

At birth the child was oedematous, cyanosed and apnoeic. Attempts at resuscitation were followed by only two or three shallow gasps.

Radiological Investigation.

ANTENATAL EXAMINATION. The patient was referred for radiological examination (to exclude foetal abnormality or twin pregnancy) on September 22, 1959; the height of the fundus corresponded to that normally expected at 34-35 weeks; by dates, the maturity was 27 weeks. One foetus was present in a vertex L.O.A. position, with evident hydramnios in considerable degree. The foetal stature corresponded to that expected for a maturity of 27-28 weeks. The attitude of the foetus, both of the trunk and the limbs, was reminiscent of that often found in hydrops foetalis and at least suggested the presence of some foetal abdominal distension.

POSTNATAL EXAMINATION. Radiographs (Figs. 1 and 2) were taken of the whole infant shortly after its death which occurred at 10 minutes after birth. It was evident that air had been both swallowed and inhaled. There was slight distension of the abdomen but this was not due to intestinal gas. The thorax presented most unusual appearances. There was a right pneumothorax with a complex loculated appearance peripherally. The margin of this pneumothorax extended well across to the left of the mid-line and no pulmonary aeration was observed on either side. The volume occupied by the left lung was evidently much reduced. The cardiac outline could not be separately discerned. Thus the appearances bore some resemblance to those found in a tension pneumothorax on the right side, but the opacity due to the compressed lung was much greater than would be expected.

Necropsy. This revealed a premature male infant weighing 1,550 g. whose crown-rump length was 28 cm. and crown-heel length was 39 cm. There was marked oedema of the arms and back and the abdomen was distended. There were no other abnormalities seen on external examination. The pleural sacs contained no

FIG. 1.—Radiograph. Antero-posterior view showing right-sided pneumothorax. There is a cystic space containing air in the mass in the right lung. The mediastinum is displaced to the left.

FIG. 2.—Radiograph. Lateral view. Air can be seen in the small intestine.

excess fluid. There was a pneumothorax on the right side which was under tension. The pleurae were glistening. The larynx, trachea and main bronchi were normal. A large, firm, pink, nodular mass involved the upper lobe of the right lung (Fig. 3). On slicing, several cystic cavities were opened (Fig. 4). The mass was approximately three times the usual size of the right upper lobe. A probe could be passed from the right upper lobe bronchus into one of the cysts. The malformation was so large that it had herniated across the midline. The left lung and the middle and lower lobes of the right lung were hypoplastic. The pericardial sac contained no excess fluid. The heart was of the expected size and there were no congenital abnormalities of either the heart or great vessels but the organ was displaced to the left. There was a moderate excess of clear, yellow fluid in the peritoneal sac. The tongue, pharynx, oesophagus, stomach and intestines were normal. The liver was of the expected size and appeared macroscopically normal. The bile passages were patent. The falx cerebri and tentorium cerebelli were intact. There was a small amount of blood diffusely spread in the subarachnoid space over both cerebral hemispheres and over the cerebellum. The brain and choroid plexuses were congested. The adrenals (each 1·5 g.), pituitary, thymus and thyroid glands were normal. The kidneys (each 8 g.) showed foetal lobulation. The ureters, bladder and external genitalia were normal. The placenta weighed 370 g. and measured 17 × 14 cm. The placental/foetal weight ratio was 1:4·1. There was a velamentous insertion of the cord. The membranes were complete. The placenta was not oedematous and appeared normal on slicing.

Histology.

UPPER LOBE OF RIGHT LUNG. The pleura showed little change. The mass consisted of innumerable small acini lined by a low cuboidal epithelium (Fig. 5). They were separated from one another by a loose connective tissue stroma which contained elastic fibres. Some larger cystic spaces lined by columnar epithelium were also present. These were surrounded by smooth muscle 1-3 layers thick. These structures had the appearance of terminal bronchioles and some showed very marked dilatation (Fig. 6). There was no evidence of cartilage formation in the wall of any of the bronchial-like structures and no glands were present in their submucosa. In a number of areas there were collections of several acini lined by tall, columnar, mucus-secreting epithelium (Fig. 7). The material in the lumen of these

FIG. 3.—Large mass replacing the upper lobes of the right lung. A ruptured cyst is seen in the centre. The left lung is extremely hypoplastic.

FIG. 4.—Section of the mass showing several large cysts. The middle and lower lobes of the right lung are hypoplastic.

structures gave a strongly positive reaction when stained by the periodic acid-schiff technique. The appearance of the mass was consistent with a diagnosis of congenital adenomatoid malformation. There was no subdivision of the mass into lobules. There was a sharp demarcation at the lower border of the mass between malformed tissue and adjoining hypoplastic lung (Fig. 5). A narrow connective tissue septum appeared to separate the one from the other.

MIDDLE AND LOWER LOBE OF RIGHT LUNG. The pleura was healthy. The lobes showed marked hypoplasia and were unexpanded. The bronchi, bronchioles, alveolar ducts and alveoli showed no structural lesion.

LEFT LUNG. This lung was also extremely hypoplastic. The bronchial structure appeared to be normal.

No lesion was found on histological examination of the other organs.

Discussion

Willis (1958) defined hamartomas as tumour-like, but primarily non-neoplastic malformations or errors of tissue development. characterized by abnormal mixture of tissues indigenous to the part with excess of one or more of these. On these grounds he does not consider 'chondromatous hamartomas' of the lung to be malformations but true tumours. Nevertheless, cartilage-containing

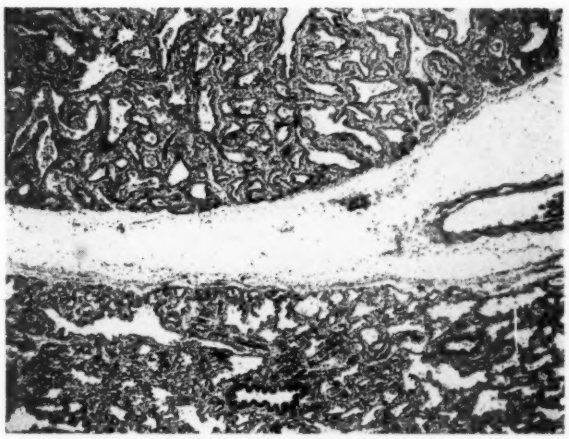

FIG. 5.—Showing adjacent areas of hamartoma (above) and hypoplastic lung. H. and E. × 26.

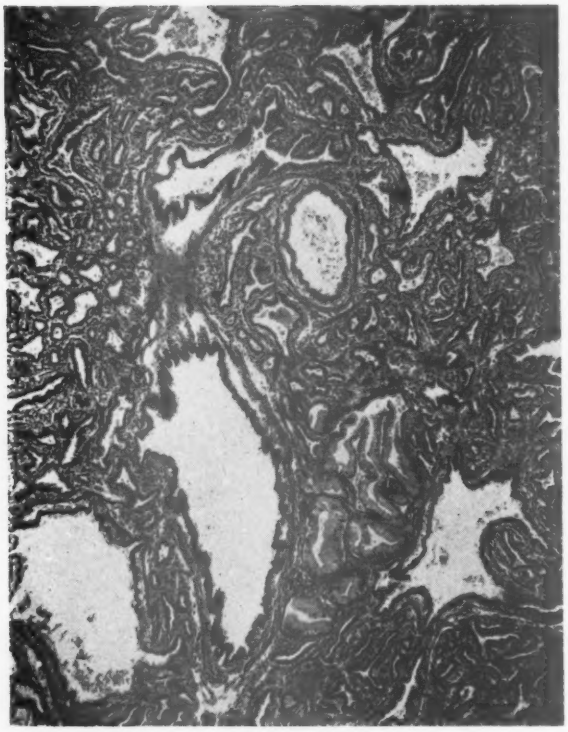

FIG. 6.—Malformation showing large cystic spaces lined by respiratory epithelium and surrounded by some layers of smooth muscle. A focus of mucus secreting epithelium is present. H. and E. × 48.

FIG. 7.—High power view of part of field in Fig. 3 showing detail of mucus secreting tissue. H. and E. × 103.

hamartomas are occasionally found in the lungs of infants. Jones (1949) described such a case in which there was an admixture of foetal lung tissue, cartilage and fibrous tissue which had replaced part of one lung of an infant. The appearances were not those of a neoplasm but of a malformation of lung tissue, and the author suggested that this was a true cartilage-containing hamartoma. As well as the more solid type of hamartoma such as described by Harris and Schattenberg (1942), Willis includes congenital cystic disease in this class of disorders of the lungs. Klosk, Bernstein and Parsonnet (1946) define cystic disease of the lung as 'any condition in which the lung parenchyma is replaced by sharply defined cavities containing fluid or air'. These authors divide this disease into the variety which exhibits solitary large cysts and that characterized by multiple cysts. Herrmann *et al.* (1959) describe an acquired type. The cysts in the congenital form of the disease are lined by pseudo-stratified ciliated columnar epithelium or respiratory cuboidal epithelium. In the more common form of cystic disease of the lung, however, cartilage is present in the bronchial wall. It is notably absent in adenomatoid malformation. Histological examination of the lung in this case showed small cystic spaces lined by a low columnar epithelium of the respiratory variety in most areas. Other parts of the hamartoma contained spaces lined by cuboidal and tall columnar epithelium. Levine (1950) postulates that this form of hamartoma arises by pinching off of portions of the main lung buds and their derivatives in the second half of intrauterine life. Some of these portions of bronchial tissue may completely separate from the bronchial tree and continue to secrete fluid which will distend the cysts. Other portions do not completely separate but maintain a narrow communication with the bronchi. In our case, we were able to pass a probe from a main bronchus into one of the larger cysts. This apparently supports Levine's suggestion as to their mode of origin. Herrmann *et al.* (1959) mention, in addition, a second possible mode of origin, namely a disturbance occurring in the fourth foetal week. At this time two septa divide the foregut into an anterior and posterior part. If cells from this region detach themselves at about this period, then bronchial or gastric cysts would arise. The occurrence of cystic spaces lined by mucus secreting epithelium

has been noted by previous authors (Ch'in and Tang, 1949; Koboth, 1936) and this suggests that the anomaly may have its origin during the fourth foetal week. Craig *et al.* (1956), however, regard these as aberrant forms of bronchial mucous glands. Conway (1951) believes congenital cystic disease of the lung is the result of some unknown process which interferes with canalization at some point proximal to the termination of the lung bud. Distal to this point canalization begins again producing an isolated canalized segment lined by normal bronchial mucosa. In adenomatoid hyperplasia there is a great increase in the number of structures which have the appearance of terminal bronchioles. The smaller spaces lined by cuboidal epithelium probably represent incompletely formed alveolar ducts.

At necropsy the hamartoma is usually found to increase both the size and weight of the affected lung (the increase in bulk often causing herniation of the lung across the midline with mediastinal displacement) both of which occurred in the present case. In most cases, only one lobe of the lung is affected; indeed, we have found records of only two cases in which an entire lung was involved (Wolman, 1930; Goodyear and Shillitoe, 1959). We have found no preference for the right or left lung and for upper, lower or middle lobes. On slicing the abnormal tissue mass, cysts of varying size are usually seen lying in firm, pale, macroscopically homogeneous tissue. Our case showed relatively few cysts. We found no cartilage in the affected part of the lung and this favours the theory of a valve-like mechanism by which air can enter the spaces of the hamartoma during inspiration but, because of lack of supporting tissue around the communicating channels with the bronchi, air is trapped during expiration. In this way the size of the malformation progressively increases after birth and the 'expanding lung syndrome' is produced. This causes not only displacement of the mediastinum but distortion of the venae cavae and maldevelopment of the contralateral lung. In our case, not only was there hypoplasia of the lung on the opposite side, but of the other lobes of the ipsilateral lung. As in previously reported cases we found no congenital abnormality in any other part of the body.

The diagnosis of this condition is not without difficulty, but, in the present case, foetal abnormality was first considered when hydramnios developed in the 27th week of pregnancy. This is a common feature of cystic disease of the lung, but is unique in that hydrops foetalis was diagnosed by a maternal pelvic radiograph during pregnancy. Ch'in and Tang (1949) and Gottschalk and Abramson (1957) suggest that the hydramnios is due to cardiovascular disturbance in the foetus following mediastinal and vena caval displacement by the tumour. This is postulated to produce an increase in systemic venous pressure resulting in not only hydrops foetalis but hydramnios. There seems to be little evidence that the oedema is the result of cardiac failure. Generalized anasarca is less common in foetuses with this malformation delivered at term or in infants who live for some time after birth (Craig *et al.*, 1956).

Children suffering from this disease are usually premature; presumably the early labour results from hydramnios. Ch'in and Tang's series consisted mainly of premature and stillborn foetuses, and other cases reported up to 1943 were either stillborn or died in early neonatal life. The mother of our case went into labour at 28 weeks and spontaneously delivered a moderately oedematous and cyanosed infant. Oedema is not unusual in this condition (Grawitz, 1880; Ch'in and Tang, 1949; Craig *et al.*, 1956) and, as mentioned above, is probably due to vena caval distortion. Thus hamartoma of the lung should be borne in mind in the differential diagnosis of cyanosis and oedema in a premature infant.

Tension pneumothorax may result from this malformation (Herrmann *et al.*, 1959), although the vast majority of cases result from rupture of an emphysematous bulla on the surface of the lung or (in slightly older infants) staphylococcal bronchopneumonia. Our case was unusual in that rupture of an air-containing cyst had occurred following attempts at resuscitation.

The cases of Fischer, Tropea and Bailey (1943), of Graham and Singleton (1955), the four cases of Craig *et al.* (1956) and the four cases of Herrmann *et al.* (1959) were all diagnosed during life by radiological examination. This investigation should be performed in all cases in which pulmonary hamartoma is considered as a possible diagnosis.

In retrospect, it seems evident that the loculated appearance in the radiograph of our case was due to air in the superficial cystic parts of the tumour and that a marginal rupture had occurred leading to the pneumothorax. Whilst the limits of part of the tumour were surely outlined, it was not possible to differentiate between the tumour and the atelectatic right lung.

Treatment of this condition is removal of the affected tissue. As the child continues to breathe the cysts in the malformed lung increase in size and progressive displacement of the mediastinum with compression of the contralateral lung occurs. Thus early treatment is imperative, and this, in

turn, depends on early radiological diagnosis of the disease. Our case was complicated by a tension pneumothorax and hypoplasia of all the lung tissue not involved in the hamartoma. The period of survival was insufficient to permit surgical intervention.

Summary

A case of hamartoma of the lung is described in an infant who survived for 10 minutes after delivery. The remaining lung tissue was hypoplastic. A tension pneumothorax was present on the same side as the lesion.

Foetal abnormality was suspected during pregnancy on account of hydramnios. Radiological examination revealed a hydropic foetus. At necropsy a large mass was found replacing the upper lobe of the right lung. On histological examination the mass was found to be composed of multiple small cysts and spaces lined by respiratory type epithelium.

The relationship between congenital cystic disease of the lung and true pulmonary neoplasm is discussed.

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PULMONARY INFECTIONS IN CHILDREN WITH A PARTIAL THORACIC STOMACH ('HIATUS HERNIA')

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During the early stages of a clinical study of the partial thoracic stomach ('hiatus hernia') in children a number of patients were seen who appeared unduly susceptible to pulmonary infections. This observation suggested a possible relationship between the two conditions. The following review was undertaken with the object of either proving or disproving this contention.

Method

The impossibility of obtaining for comparison figures relating to the incidence of pulmonary infections in the childhood population and the lack of objective data upon which to base conclusions presented two major difficulties in carrying out this survey. It was considered that these difficulties could be largely overcome if a suitable sub-division of patients was devised making it possible to compare two groups of children within the series. Such a procedure would dispense with the need of a control group for comparison and, at the same time errors inevitably introduced as a result of varying interpretations of the terms 'bronchitis' and 'pneumonia' would be largely eliminated as these would theoretically occur with equal frequency in either group.

Of necessity, the data for this analysis have been largely derived from the clinical history obtained from parents. A statement to the effect that the child had had either 'bronchitis' or 'pneumonia' as diagnosed by the family doctor has been accepted as a pulmonary infection for the purpose of this survey.

Should there exist a tendency for children with a partial thoracic stomach to develop pulmonary infections it seemed logical to infer that such infection might be related either to the type or frequency of symptoms associated with the patient's gastro-oesophageal abnormality. For this reason the severity of the gastro-oesophageal symptoms has been used as a basis for analysing the data relating to these patients. The following two symptom groups have been defined based on a previous classification (Carré, 1959):

Group X: Vomiting and/or difficulty in swallowing solid food occurring on average more frequently than once a month.

Group Y: Vomiting and/or difficulty in swallowing solid food occurring on average less often than once a month.

Such a classification, however, does not provide for a clearcut sub-division of patients because of the symptomatic improvement shown by the majority with advancing age (Carré, 1959). It is apparent that at a particular age a child's symptoms might conform to Group X severity but a year later be those of Group Y. To overcome this difficulty each patient has been classified as having symptoms of either Group X or Y severity for each year of age. For example, a child who suffered from frequent symptoms for more than six months of the age period 1-2 years would be classified under Group X for that period, and similarly would be reclassified under Group Y for the age period 2-3 years if symptoms had subsided to conform with this grouping.

In this way two series of 12 monthly age periods have been obtained. On the one hand a series consisting of annual periods during the major portion of which symptoms of Group X severity were recorded and on the other hand a series of annual periods during which less troublesome symptoms were noted (Group Y). In addition, the occurrence of pulmonary infections, night vomiting and dysphagia with solid food have been recorded in respect of each annual age period.

Selection of Patients

Children considered in this survey all had a small portion of stomach protruding into the chest through the oesophageal hiatus. The gastro-oesophageal junction was in every instance situated along the upper border of the intra-thoracic gastric

TABLE 1
ASSOCIATION OF PULMONARY INFECTION WITH FREQUENCY AND TYPE OF VOMITING

Age Period (years)	Clinical Group	No. of 12-monthly Age Periods	No. of 12-monthly Periods During which Following Symptoms were Noted				
			Pulmonary Infection	Dysphagia	Dysphagia and Pulmonary Infection	Night Vomiting	Night Vomiting and Pulmonary Infection
1–2	X	37	15	13	2	30	15
	Y	41	2	2	0	3	0
2–3	X	22	6	7	1	14	5
	Y	52	8	2	1	5	1
3–4	X	19	5	12	4	13	4
	Y	30	4	2	0	2	0
4–5	X	9	0	5	0	4	0
	Y	18	2	1	0	4	1
1–5	X	87	26	37	7	61	24
	Y	141	16	7	1	14	2

Group X Attacks of vomiting and/or dysphagia occurring more frequently than once a month during at least six months of any one year of age.

Group Y Fewer symptoms than Group X.

loculus. Surgically treated patients have been excluded.

As it was intended to compare the occurrence of pulmonary infections with specific clinical disturbances, such as night vomiting and difficulty in swallowing solid food, the age period reviewed has been restricted to over 1 year, when both these features could be more accurately determined. With relatively few children over 5 years available for study this age has been adopted as the upper limit for consideration.

Except where specifically stated the following analysis is restricted to patients who had no associated oesophageal stricture. Information relating to 78 patients has provided 228 annual periods for analysis.

Results

A pulmonary infection was recorded for 26 of the 87 annual age periods (29·9%) during which symptoms were classified as of Group X severity and for 16 of 141 periods (11·3%) during which symptoms were minimal, Group Y (Table 1). This difference in incidence is statistically significant ($p < 0{\cdot}001$).* These observations confirm that pulmonary infections are commoner in children with a partial thoracic stomach during periods when vomiting is frequent.

In theory this significantly higher recorded incidence of pulmonary infections during Group X annual periods could be related not to the frequency of symptoms but to the occurrence either of dysphagia with solid food or night vomiting, both of which were frequently noted clinical features during these periods. To test this hypothesis a further analysis of Group X periods has been undertaken as follows.

Difficulty in swallowing solid food was a recorded symptom during 37 of the 87 Group X annual periods; a pulmonary infection was recorded during seven of these 37 periods (18·9%). The comparable figures for periods during which dysphagia was not a complaint were 19 of 50 (38%). However, when annual periods were excluded during which night vomiting was also a feature these figures become two of 19 (10·5%) and none of seven respectively. Information relating to patients with an associated oesophageal stricture has been analysed in a similar manner. In all these children the predominant and often only symptom was difficulty in swallowing solid food. In only four of 37 annual periods was a pulmonary infection noted, an incidence of 10·8%. Allowing for the small figures involved, these latter estimates (10·5, 0 and 10·8%) conform with the observed frequency of pulmonary infections during the Group Y periods (11·3%) when clinical disturbances were judged to be infrequent. The occurrence of dysphagia therefore appears to have no direct bearing on the increased incidence of pulmonary infections noted during periods of frequent symptoms.

On the other hand, a pulmonary infection was recorded during 24 of 61 annual Group X periods (39·3%) during which night vomiting was a feature. The comparable figures for Group X periods during which night vomiting was not a complaint were two of 26 (7·7%). This difference is statistically significant ($0{\cdot}01 > p > 0{\cdot}001$). Furthermore, the frequency of pulmonary infections during Group X periods when night vomiting was not recorded (7·7%) is similar to that estimated for Group Y (11·3%).

Radiological Observations

Segmental pulmonary lesions have been identified radiologically on 19 occasions in 17 of 242 children with a partial thoracic stomach (Table 2). These lesions were confined to the right lung in 13 and the left in four; in two instances both lungs were involved. A single lobe was involved in 16 instances. In 10 of the 12 right-sided lesions the affected area was either the middle or upper lobe. Of the four left-sided lesions the upper lobe was the affected site in two.

At the time of demonstrating these lesions eight patients were aged less than 12 months, seven were between 1 and 3 years old and four were more than 3 years of age.

TABLE 2

RADIOLOGICALLY CONFIRMED PULMONARY LESIONS

Patient	Lobe of Lung Affected (Collapse/Consolidation)	Age (yrs)	(mths)
T.B.	R.U.		10
A.S.	R.M.	7	2
E.W.	L.U.	1	3
D.Ru.	R.L.		11
	L.U.	1	9
R.Ha.	R.M.		2
R.Gi.	R.M. and L.U.	1	1
	R.M.	1	4
M.W.	L.L.	4	6
W.J.	R.M.	1	2
C.N.	R.M.		3
S.G.	R.M.		2
A.S.	R.U.		7
P.W.	R.U.		2
M.L.	L.U. and R.M.	3	1
J.D.	R.L. and R.M.	7	0
J.M.	L.L.		8
D.H.	R.M.	2	5
S.S.	R.L.	2	9

Lobe affected: R.U. = right upper R.M. = right middle
R.L. = right lower
L.U. = left upper L.L. = left lower

* In all quoted statistical analyses $p < 0{\cdot}05$ has been accepted as evidence of significance.

Discussion

It has been shown that in children with a partial thoracic stomach the risk of acquiring a pulmonary infection is greatly increased if vomiting at night is a symptom. In the present study the occurrence of night vomiting was associated with more than a threefold increase in the number of recorded pulmonary infections. On the other hand no relationship could be demonstrated between the development of pulmonary infections and either frequent day vomiting or dysphagia with solid food.

These findings suggest that many of the pulmonary infections recorded in children with a partial thoracic stomach result from the inhalation of vomited material at a time when the patient is in a semi-conscious state. The radiological observations recorded in this study are interpreted as supporting such a contention. These show a preponderance of single lobe lesions with the right lung principally affected, a distribution demonstrated by Brock, Hodgkiss and Jones (1942) as characteristic of the inhalation of foreign material during recumbency. However, an unusually large number of right middle lobe lesions were noted in the present series. This may be due to the fact that while still only half awake many patients will sit up and lean forward when vomiting thereby assuming a posture suited to the inhalation of material into the right middle lobe bronchus (Foster-Carter, 1943).

Radiographically defined pulmonary lesions were most frequently noted in patients under 3 years of age. In view of the association between night vomiting and pulmonary infections these findings are to be expected as most children with a partial thoracic stomach suffer from progressively fewer gastro-oesophageal symptoms (including night vomiting) as they grow older (Carré, 1959).

Summary

A study is described in which the occurrence of pulmonary infections in children with a partial thoracic stomach has been related to specific symptoms referable to the patient's gastro-oesophageal abnormality. The results indicate that the incidence of pulmonary infections in children with a partial thoracic stomach is considerably increased if night vomiting is a symptom. On the other hand there is no reason to believe that frequent day vomiting or difficulty in swallowing solid food predispose to the development of pulmonary infections.

Evidence is quoted in support of the view that many of the pulmonary infections noted in patients with night vomiting result from the inhalation of vomited material.

I am greatly indebted to Dr. R. Astley of the Children's Hospital, Birmingham, and Dr. F. Plarre of the Royal Children's Hospital, Melbourne, Australia, for the radiological assessment of the patients considered in this study. I wish to thank also the consultant physicians and surgeons of the Children's Hospital, Birmingham, the Royal Children's Hospital, Melbourne, and the Royal Belfast Hospital for Sick Children for permission to review their patients and Mr. J. D. Merrett of Queen's University, Belfast, for help with the statistical analysis.

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THE FATE OF THE PARTIAL THORACIC STOMACH ('HIATUS HERNIA') IN CHILDREN

BY

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In a previous communication it was estimated that about two of every three clinically affected infants with a partial thoracic stomach cease vomiting spontaneously before 2 years of age in the absence of either postural or surgical therapy (Carré, 1959). What then happens to the gastro-oesophageal abnormality in such children? Does the partial thoracic stomach undergo anatomical restitution?

Evidence has been presented elsewhere confirming the value of adequate postural therapy in the management of infants with a partial thoracic stomach (Carré, 1957). What, however, is the effect of such treatment on the radiological 'cure' rate? The present review is aimed at answering these questions.

Observations

Three studies are included and each is considered separately.

1. A retrospective reassessment of patients given neither postural nor surgical treatment.
2. A prospective follow-up of similarly untreated patients.
3. A prospective follow-up of clinically affected infants treated by adequate sustained posture.

All children considered in this survey had a small loculus of stomach protruding through the oesophageal hiatus into the chest. The gastro-oesophageal junction was situated in every instance along the upper border of the intrathoracic portion of stomach. Children with gastro-oesophageal incompetence but no definite intrathoracic gastric loculus (i.e. 'chalasia') have not been included.

Retrospective Review of Untreated Patients. The following review is based on a study undertaken at the Children's Hospital, Birmingham, during 1951-53. There seemed then no reason to suppose that the increase in the number of children recognized as having a partial thoracic stomach reflected anything more than improved diagnosis and a greater awareness of the condition. This being so, it was argued that provided the abnormality persisted, even despite cessation of symptoms, it should be possible to recognize such cases in retrospect. The following retrospective follow-up study was therefore undertaken.

Hospital case records relating to patients admitted to the Children's Hospital, Birmingham, during the 10 years, 1941-50 inclusive, because of either vomiting of uncertain cause or vomiting ascribed to feeding difficulties, pylorospasm, 'habit' or 'cyclical' vomiting and peptic ulceration were examined. Patients whose listed clinical features and progress appeared similar to those of children with a proven partial thoracic stomach were selected for review. In addition, all patients admitted to hospital during the 20-year period 1930-50 and diagnosed as having a lower oesophageal abnormality were included for clinical and radiological reassessment.

One hundred and forty-seven patients were selected for review. Three children were unable to attend for examination, six others had died and 21 (14·3%) remained untraced. All 117 children who attended were examined by one of us (I.J.C.) and the clinical history re-evaluated. These children were then examined radiologically. At the time of examination the radiologist (R.A.) was kept in ignorance of the clinical history obtained. He was aware, however, that all children being examined as part of this investigation had previously attended hospital because of vomiting.

At the time of their reassessment patients were divided into two groups. One consisted of children whose clinical progress appeared on re-evaluation to have conformed with the general pattern observed in children with a proven partial thoracic stomach; children in this group were considered on clinical grounds as likely to show abnormal radiological findings. Children in the second group were

assessed as having atypical clinical histories and therefore unlikely to show any gastro-oesophageal abnormality on radiological examination. Subsequent comparison of the radiological and clinical findings showed a high degree of correlation. A partial thoracic stomach was demonstrated radiologically at the first examination in 35 of the 52 children selected on clinical grounds as likely to have this abnormality. In an additional eight, free gastro-oesophageal reflux was demonstrated but no intrathoracic loculus of stomach could be defined with certainty. The radiological appearances in the other nine children appeared 'normal'. In only four of 65 children in the second group was a partial thoracic stomach demonstrated. Sixty-one were classified as showing no radiological abnormality.

In view of extremely suggestive clinical histories, 12 of the 17 children in whom a definite partial thoracic stomach could not be defined, were re-examined radiologically. On this second occasion a small partial thoracic stomach was demonstrated on fluoroscopy in two children previously noted as having free gastro-oesophageal reflux only and in one of those considered 'normal'. The results of these observations are shown in the Table.

TABLE
RETROSPECTIVE FOLLOW-UP REVIEW

Likelihood of Partial Thoracic Stomach from Clinical Assessment	Number of Patients	Radiological Findings		
		Positive	Doubtful (Gastro-oesophageal Reflux only)	Considered 'Normal'
Probable	52	38	6	8
Unlikely	65	4	0	61
	117			

Of 52 patients whose early progress was considered typical of that of children with a partial thoracic stomach, 44 were free of troublesome symptoms when seen, i.e. vomiting and/or dysphagia occurred less than once a month. A partial thoracic stomach was demonstrated radiologically in 30 of these 44 patients; 10 of these had been virtually free of symptoms from infancy. These patients had first attended hospital some two to 18 years previously.

Prospective Follow-up of Untreated Patients. Almost every child with a partial thoracic stomach seen since 1951 has been treated by either posture or surgery. For this reason, few patients are suitable for consideration. Only untreated patients in whom a partial thoracic stomach was recognized before 2 years of age have been considered. Of these, 10 have been re-examined by barium swallow and fluoroscopy at least two years after cessation of symptoms. A partial thoracic stomach was still demonstrable in eight. In five patients the follow-up was of five years or more; a definite partial thoracic stomach was seen in three.

Prospective Follow-up of Clinically Affected Infants treated by Adequate Sustained Posture. Twenty patients who were first started on adequate sustained postural treatment before 3 months of age were free of symptoms at the time of their last examination by barium swallow and fluoroscopy. All these patients had been maintained in a sitting posture throughout the 24 hours for at least six months. At the time of their examination these children had been free of symptoms for periods varying from two to seven and a half years. An intrathoracic gastric loculus was still demonstrable in 13. Ten children had been free of symptoms for more than five years; a partial thoracic stomach was defined in seven of these.

Discussion

During the 'retrospective' follow-up investigation of patients with a partial thoracic stomach the opportunity was taken to record independent clinical and radiological observations. A very high degree of correlation was obtained, thereby further confirming the specific nature of the clinical disturbances.

The investigation included the examination of 44 virtually symptom-free persons who had suffered from symptoms during infancy and early childhood comparable to those experienced by patients with a partial thoracic stomach. In 17 no gastro-oesophageal abnormality was demonstrated on the first fluoroscopic examination. Nonetheless, the early clinical progress of these 17 patients had been so similar to that of patients with a partial thoracic stomach that it was our belief that they too had had an identical gastro-oesophageal abnormality. The demonstration of a partial thoracic stomach in three of 12 individuals who were re-examined tends to confirm such an assumption. If it is accepted that the clinical disturbances suffered by all 44 patients during their infancy and early childhood were related to the presence of a partial thoracic stomach, then the incidence of spontaneous radiological 'cure' (i.e. failure to demonstrate a gastro-oesophageal abnormality) among these individuals may be assessed as about one in three (14 of 44). Confirmation of these deductions is provided by the

'prospective' follow-up review of untreated patients in which a similar radiological 'cure' rate was obtained.

The radiological 'cure' rate of one in three (seven of 20) among infants treated conservatively is comparable to that computed for untreated patients. There is therefore no evidence from this study that postural treatment results in an increased incidence of radiological 'cure'.

The observations recorded in this review further confirm our previously expressed opinion that despite cessation of symptoms a partial thoracic stomach will remain fluoroscopically demonstrable during childhood in the majority of instances (Carré, Astley and Smellie, 1952). More recently Swyer (1955), Guichard, Verger and Humeau (1956), Masse and Bader (1957) and Burke (1959) have reported similar observations.

Evidence has been quoted both in this and in a previous communication (Astley and Carré, 1954) showing that a negative radiological examination does not necessarily exclude a partial thoracic stomach. Plarre (1956) has also stressed this fact. Thus, the negative radiological findings recorded in about a third of our symptomless patients should not be interpreted as proof of anatomical cure.

We are grateful to the consultant physicians and surgeons of the Children's Hospital, Birmingham, for permission to examine and follow-up their patients.

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THE BACTERIAL FLORA OF THE STOMACH AND SMALL INTESTINE IN CHILDREN WITH INTESTINAL OBSTRUCTION

BY

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The alimentary tract at birth is either sterile or contains only a few micro-organisms (Wilson and Miles, 1955). Within a few days of birth a profuse flora is established in the mouth and large intestine. However, the small intestine remains relatively free from micro-organisms throughout life (Cregan and Hayward, 1953; Anderson and Langford, 1958a). Thus in health it seems that some antibacterial mechanism is present which prevents a resident flora from becoming established in the small intestine.

The nature of this antibacterial mechanism is obscure. Cregan, Dunlop and Hayward (1953) have shown it to be independent of the gastric germicidal barrier. Anderson and Langford (1958a) have previously suggested that maintenance of normal intestinal motility is important. Evidence for this suggestion has been sought in the present study, which is an investigation of the flora of the small intestine in conditions where intestinal motility is affected by obstruction to the onward passage of intestinal contents. The patients examined included newborn and older children with obstructive lesions of differing aetiology and duration at differing sites along the small intestine.

A search of the literature did not reveal any previous investigation in newborn or older children or even any thorough investigation of the intestinal flora in adults with intestinal obstruction. Therefore this paper will also describe the extent and nature of the flora of the small intestine in children with intestinal obstruction. The results of a similar study in adults are reported elsewhere (Bishop and Adcock, 1960).

Material and Methods

Clinical Material. Twelve newborn babies aged from 1 to 7 days, in whom obstruction had been present at birth, were examined. These patients included one with volvulus of the stomach, two with duodenal atresia, three with jejunal atresia, one with Hirschsprung's disease and five with meconium ileus.

In addition 12 children aged from 10 days to 13 years in whom obstruction had developed acutely and one child of 17 months with subacute obstructive symptoms since birth were examined. The pathological conditions responsible for the obstruction and the duration of obstruction before operation were extremely varied and are recorded in Table 1.

Clinical findings relevant to the investigation were recorded for each patient on a specially compiled proforma. The data sought included duration and character of any vomiting, time of the last bowel action, details of any preoperative antibiotics and a description of the findings at operation.

Collection of Specimens. Specimens of intestinal contents were obtained in the following order from patients during operation for relief of the obstruction: from stomach via Ryle's tube; swab of free fluid in the peritoneal cavity; from small intestine approximately 10 cm. distal to obstruction; from small intestine approximately 10 cm. proximal to obstruction; from other levels of small intestine proximal to the obstruction, depending on the level of obstruction.

The contents of the small intestine were sampled using the following direct needling technique originally described by Cregan and Hayward (1953). At operation 2 ml. of sterile Ringer's solution were injected into the lumen of the bowel which was washed with this fluid by gently sucking back and forth with the syringe. The resultant diluted intestinal contents were then withdrawn. In order to keep the technique of sampling uniform, this procedure was always used even when the obstructed intestine contained sufficient fluid for direct aspiration.

Bacteriological Examinations. Usually within three hours of collection two drops (about 0·06 ml.) of each specimen were inoculated on to each of the following media: horse blood agar and plain desoxycholate agar incubated aerobically at 37° C.; horse blood agar incubated anaerobically at 37° C. with 5-10% added CO_2. The range of media and conditions of incubation

TABLE 1

BACTERIAL FLORA IN INTESTINAL OBSTRUCTION IN BABIES AND OLDER CHILDREN

Case No.	Age	Cause of Obstruction	Duration of Obstruction (days)	Stomach	Duodenum		Jejunum		Ileum		Colon
					Above	Below	Above	Below	Above	Below	
1	6 days	Volvulus of stomach	6	±O±F							
2	4 days	Duodenal atresia	4	±O	±O	■					
3	5 days	Duodenal atresia	5	±O	±O	■					
4	17 mths	Duodenal stenosis	(17 mths subacute)	■	■	nt					
5	7 wks	Adhesions following Ramstedt's operation	8 hours	±O±F	nt		±F	nt			
6	1½ days	Jejunal atresia	1½	+++F	nt		+++F	■			
7	4 days	Jejunal atresia	4	+++F	nt		+++F	■			
8	5 days	Jejunal atresia	5	+++F	nt		+++F	■			
9	10 days	Universal mesentery with volvulus	12 hours	nt	nt		++F		+++F	nt	
10	13 yrs	Adhesion	1	±O	nt		nt		+++F	nt	
11	4 wks	Band obstruction from Meckel's diverticulum	1	nt	nt		nt		++F	++F	
12	3 mths	Inflammation of Meckel's diverticulum with stenosis of ileum	1½	■	nt		nt		+++F	++F	
13	2 days	Meconium ileus	2	■	nt		■		■	nt	
14	2 days	Meconium ileus	2	nt	nt		■		++F	■	
15	7 wks	Intrauterine perforation and peritonitis, subsequent stenosis of ileum	2	+++F	nt		+++F		+++F	■	
16	6 yrs	Appendicular abscess	3	nt	nt		+++F		+++F	+++F	
17	3½ days	Meconium ileus	3½	+++O+++F	nt		+++O+++F		+++O++F	nt	
18	3½ days	Meconium ileus	3½	+O	nt		+++F		nt	■	
19	3 mths	Postoperative adhesions	4	++F	nt		nt		+++F	■	
20	8 yrs	Adhesions from appendicitis	5	nt	nt		nt		+++F	■	
21	7 days	Meconium ileus	7	nt	nt		+++F		±F	nt	■
22	3 yrs	Intussusception	18 hours	nt	nt		nt		+++F		
23	13 yrs	Caeco-colic intussusception	18 hours	nt	nt		nt		±O++F		
24	6 mths	Caeco-colic intussusception	1	nt	nt		nt		++F		
25	4 days	Hirschsprung's disease	4	±O	nt		+++F		+++O++F		

The vertical line in heavy type denotes level of obstruction.
O denotes a flora of oral type.
F denotes a flora of faecal type.
Plusses indicate degree of growth: ± and + denote transient flora; ++ and +++ denote resident flora (see text).
nt denotes not tested.
■ denotes sterile.

were chosen so that the growth requirements of all bacteria likely to occur in the intestinal tract would be satisfied. Direct smears were always examined as a check on the adequacy of conditions of culture. A standard plating technique was used (Cregan and Hayward, 1953) and the degree of growth was graded from ± to +++. A scanty growth (± or +) was regarded as a transient flora unable to multiply at the site sampled. A profuse growth (++ or +++) was regarded as a resident flora. As well as the plating technique, the criteria for interpretation of quantitative results described fully by Cregan and Hayward (1953) were followed exactly.

Results

Table 1 shows quantitative results from the 25 patients examined. Table 2 shows qualitative results from the 19 children with an abnormal profuse flora (++ or +++) in the small intestine. In both Tables the results from newborn and older children have been combined since no bacteriological difference between these two groups was observed.

Specimens Proximal to the Point of Obstruction. Quantitative and qualitative results from specimens proximal to the point of obstruction differed with the level of obstruction. All specimens from four children with obstruction proximal to the duodenojejunal flexure (Cases 1-4) were either sterile or contained only a scanty flora usually of oral type. By contrast in almost all (19 out of 21) children with obstruction distal to the duodenal-jejunal flexure (Cases 5-25) a profuse flora of faecal type was present in the small intestine above the point of obstruction. Stomach specimens from 12 of these children were also examined. Six yielded a profuse faecal flora and six were either sterile or yielded only a scanty flora of oral type.

Since 12 children received antibiotics parenterally before operation it was important to be sure that

TABLE 2

BACTERIAL FLORA OF THE SMALL INTESTINE IN ACUTE INTESTINAL OBSTRUCTION

Faecal Type Organisms	No. of Times Isolated	Oral Type Organisms	No. of Times Isolated
Bact. coli type I	15	*Staph. saprophyticus*	4
Cl. welchii	9	*Staph. afermentans*	2
Strep. faecalis	7	*Staph. lactis*	2
Bacteroides sp.	6	*Staph. aureus*	2
Paracolon sp.	5	*H. parainfluenzae*	2
Veillonella gazogenes	4	*Strep. agalactiae*	2
Bact. aerogenes type I	3	*Strep. mitis*	5
Bact. coli irregular type	2	*Strep. S.B.E.*	1
Bact. coli intermediate type I	2	*C. xerosis*	1
Strep. liquefaciens	2		
Strep. zymogenes	2		
Cl. fallax	1		
Cl. paraputrificum	1		
Cl. multifermentans	1		
Pr. mirabilis	1		
Pr. vulgaris	1		
Veillonella parvula	1		
Achrombacter sp.	1		
Alcaligenes faecalis	1		
Candida albicans	1		

Number of cases with abnormal resident flora = 19.

this had no effect on the bacteriological results. The antibiotics used were tetracycline or penicillin and streptomycin given intramuscularly or intravenously as one dose (Cases 6, 7, 11, 13, 14, 15 and 17) or as a more prolonged course (Cases 2, 8, 10, 16 and 19). The small intestine of five of the former and four of the latter contained a profuse faecal flora at operation, so that it is unlikely that the results from the remaining three, that yielded only scanty flora, could be attributed to suppression of bacterial growth in the bowel lumen by the preoperative parenteral antibiotics.

Specimens Distal to the Point of Obstruction. Unlike the proximal specimens, results from specimens distal to the point of obstruction were quantitatively and qualitatively independent of level of obstruction. Of 14 samples from below the obstruction, 11 were sterile. The remaining three (Cases 11, 12 and 16) yielded a profuse faecal flora but the intestinal lumen of each of these three children was only partially obstructed and it was concluded that the results were invalid due to contamination with fluid from above the point of obstruction.

Peritoneal Swabs. These specimens were obtained from eight children and were always sterile when the bowel was viable. In three children there was a portion of non-viable bowel (Cases 9, 11 and 16). In one of these (Case 9) the peritoneal swab was sterile. In the other two a faecal flora was isolated and was found to be qualitatively similar to that present in the intestinal lumen.

Qualitative Results. Table 2 shows that organisms of faecal type were common in the small intestine of the 19 patients yielding abnormal quantitative (++ or +++) results. Oral type organisms were only occasionally isolated. *Bact. coli* type I was present in 15 of the 19 children. *Cl. welchii* was present in less than half of the cases examined, an incidence much less than that found in a similar study in adults (Bishop and Allcock, 1960). None of the faecal type organisms were outside the range of those likely to occur in the healthy large intestine.

Discussion

A search of the literature of the past 60 years has not revealed any detailed investigation of the bacterial flora of the small intestine in intestinal obstruction either in children or in adults. Williams (1926, 1927) examined vomitus and small intestinal contents from adults with intestinal obstruction. However, his samples of small intestinal contents were restricted to the point of intestinal resection and the bacteriological techniques were directed mainly towards isolation of *Cl. welchii*. In the present investigation the technique of sampling allowed several levels of intestine to be examined even when no intestine was resected and the bacteriological techniques used were directed at isolating and fully identifying all species of bacteria present.

No difference was found between the results from babies and those from older children. The overall results from all children are therefore presented diagrammatically in Figs. 1 and 2. When obstruction was present proximal to the duodenojejunal flexure (Fig. 1) the small intestine and stomach remained bacteriologically normal, i.e. were either sterile or contained only a scanty flora. When obstruction was present distal to the duodenojejunal flexure a profuse faecal flora was found above the point of obstruction (Fig. 2). Regardless of the level of obstruction, small intestine distal to the point of complete obstruction remained bacteriologically

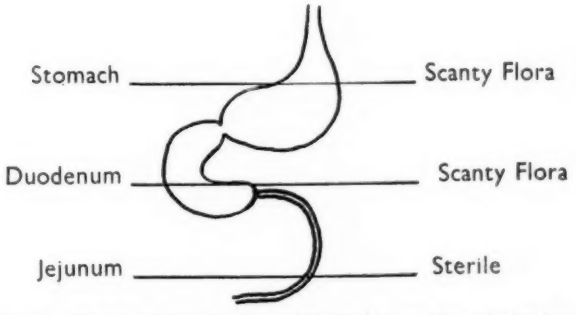

FIG. 1.—Extent of flora in gastro-intestinal tract when obstruction was in the region of duodeno-jejunal flexure.

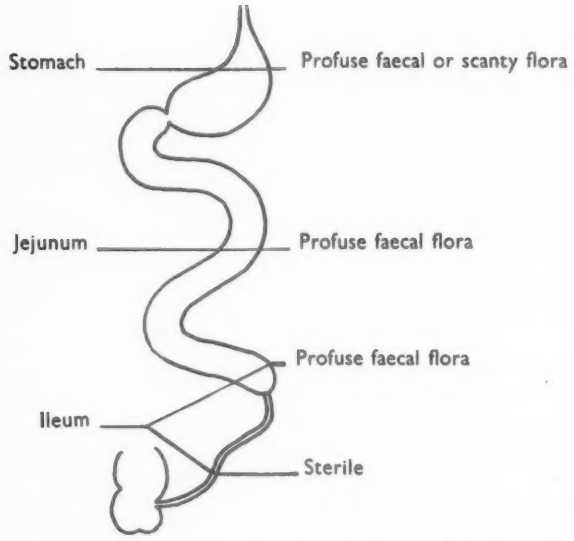

FIG. 2.—Extent of flora in gastro-intestinal tract when obstruction distal to duodeno-jejunal flexure.

normal. This was not necessarily so when obstruction was incomplete. These results indicate that the profuse faecal flora present in the small intestine above an obstruction is derived by ingestion and not by retrograde spread from the colon. This is confirmed by the results of Bishop and Allcock (1960) in adult patients.

Since the profuse faecal flora present in the small intestine above an obstruction is derived by ingestion, it follows that even in health faecal organisms frequently escape the gastric germicidal barrier and contaminate the small intestine. However, faecal organisms do not proliferate in the healthy small intestine since it has been shown to contain only a scanty flora usually of oral type (Cregan and Hayward, 1953; Cook, Elliott, Elliot-Smith, Frisby and Gardner, 1957; Anderson and Langford, 1958a). It is surprising that these organisms do not proliferate in the healthy small intestine since conditions of *p*H, of temperature and oxygen tension are favourable to their growth. Thus in health some mechanism must prevent the growth of a profuse flora in the small intestine.

The nature of this mechanism is not well understood. It has been shown to be independent of the gastric germicidal barrier (Cregan *et al.*, 1953) and therefore must depend on other factors, perhaps either chemical or mechanical, present in the small intestine. It is possible that the small intestine secretes a chemical which is either bacteriostatic or bactericidal. However, the absence of pancreatic secretion (Anderson and Langford, 1958a), or of bile (Anderson and Langford, 1958b) does not affect the flora of the small intestine and no other secretion with antibacterial activity against the species of micro-organisms isolated in this study has yet been demonstrated. If a chemical antibacterial substance exists in the small intestine it must be neutralized in some way in the terminal ileum or colon. Alternatively, it is possible that the antibacterial mechanism is dependent on mechanical factors such as constant secretion and movement of intestinal contents which might wash through all contaminating bacteria at a rate precluding colonization.

The results of this study do not allow any firm decision as to whether chemical or mechanical factors are more important. The pattern of results shown in Fig. 1 could be explained by chemical factors since it is likely that at this high level the acidity of stomach secretions is able to prevent growth of micro-organisms in the small intestine. However, the results shown in Fig. 2 could equally well be explained by disturbance of chemical or mechanical factors. The alteration in local conditions or the distension which accompanies obstruction of the small intestine could inhibit secretion of an as yet unknown chemical antibacterial substance. But it is also possible and seems more likely that the effect of obstruction on bacterial content of the small intestine could be explained by disturbance of mechanical factors alone, i.e. by the arrest of onward passage of intestinal contents and alteration of motility patterns.

From the results it is clear that parenteral antibiotics do not substantially affect the flora found above an obstruction. However, as the peritoneal swabs in those patients with non-viable bowel showed a flora of the same type as the bowel content, parenteral antibiotics may be of value in preventing peritoneal or blood spread of these organisms or of organisms spilled at operation.

Summary

The bacterial flora of the small intestine in 12 newborn and 13 older children with intestinal obstruction has been studied.

A profuse flora predominantly of faecal type was demonstrated above the point of obstruction when this was below the duodeno-jejunal flexure.

The small intestine below the site of complete obstruction was sterile.

The source of infection above an obstruction is considered to be ingestion and not retrograde spread from the colon.

The antibacterial mechanism of the small intestine is disturbed when the intestinal lumen is obstructed and reasons for this disturbance are briefly discussed.

We would like to thank the surgeons of the Royal Children's Hospital, Melbourne, for their cooperation and also the medical and surgical registrars, particularly Dr. David Danks, for their help.

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FREEZE-DRIED B.C.G.

BY

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Freeze-dried B.C.G. of British manufacture became available for experimental work in 1955. The main reason for introducing it was the need for a vaccine which would retain its potency under conditions of prolonged storage. On reconstitution for injection the vaccine should produce a uniform suspension with minimal clumping, resulting in a uniform viable bacterial count. These properties mean that tests for potency and for sterility can be performed on samples of each batch before distribution, which will be more leisurely as only surface transport is required. Centres using B.C.G. can store stocks instead of depending on week to week supplies and finally, the vaccination lesions can be more uniform and predictable, if the viable count of the vaccines remains constant for anything up to a year or longer. Experimental work in the laboratory has shown that the vaccines made in this country have fulfilled all these requirements (Ungar, Farmer and Muggleton, 1956; Ungar, 1958; Medical Research Council, 1958).

It was essential to show that freeze-dried B.C.G. was safe, would produce acceptable vaccination lesions, a high degree of tuberculin conversion within eight to 12 weeks and a positive tuberculin reaction over prolonged periods in vaccinated subjects. The optimal number of viable organisms to be injected had to be determined in order to achieve a minimal vaccination lesion with practically 100% conversion rate. The most suitable subjects for the initial clinical trials were non-contacts, because failure of conversion or a rapid reversion would not result in serious inconvenience.

Clinical trials using the technique of intradermal injection were conducted in infants by Lorber, Hart, Farmer and Muggleton (1956); Lorber, Farmer, Muggleton, Hart and Menneer (1957); Griffiths and Gaisford (1956), and in children of various ages by Lorber and Menneer (1958) and Alston, Cowell and O'Meara (1958), and in school children (13-14 years) by the Medical Research Council (1958). These clinical trials established that there was a close correlation between the number of viable organisms injected and the size of the vaccination lesions, the incidence of regional lymph-node involvement and the degree of tuberculin sensitivity following vaccination. It was apparent that reconstituted vaccines containing 10×10^6 organisms per ml. or more were unnecessarily potent and that those containing less than 1×10^6 were not sufficiently antigenic for routine use. It was also shown on controlled trials that the immediate results obtained with freeze-dried vaccines were as good as with the standard Danish liquid vaccine (Lorber *et al.*, 1957; Medical Research Council, 1958) or with the Swedish liquid vaccine (Alston *et al.*, 1958). When the number of viable organisms injected was of similar order, the vaccination lesions and the conversion rates differed very little in subjects given the dry or the liquid vaccines. As the Danish liquid vaccine had proved to be excellent both with regard to the duration of tuberculin sensitivity after vaccination (Griffiths and Gaisford, 1956; Lorber and Menneer, 1959) and its protective value against tuberculous disease in children in intimate contact with infectious tuberculosis (Lorber and Menneer, 1959), it was hoped that the freeze-dried vaccine would eventually prove to be equally efficient in these respects.

The clinical trials quoted above were concerned with the demonstration of tuberculin conversion some weeks after vaccination and with the appearance of the lesions at this stage. Since the research suggested that the best results might be obtained by a vaccine containing between 1×10^6 and 10×10^6 viable organisms per ml. of reconstituted vaccine, the manufacturers marketed such a vaccine. The Ministry accepted this vaccine as suitable for the vaccination of contacts and others and it is estimated that at present this freeze-dried vaccine is used by about half the authorities using B.C.G. in this country.

TABLE

RESULTS OF VACCINATION WITH FREEZE DRIED B.C.G. VACCINE SIX TO 12 WEEKS AND ONE YEAR AFTER VACCINATION

Batch No.	Viability Count/ml.	Results Six to 12 Weeks after Vaccination: Method of Tuberculin Testing	No. Completing Tests	No. (%) Tuberculin Positive	Local Lesion (mm.) Range	Local Lesion (mm.) Average	Tuberculin Test One Year after Vaccination: Method	No. Completing Test	No. (%) Positive
Experimental Batches									
50	$0{\cdot}14 \times 10^6$	10 T.U. O.T.	92	52 (56·5)	1–15	6	10 T.U. O.T. 10 T.U. BCG(T)	83	83 (100)
77	23×10^6	10 T.U. O.T.	114	99 (86·8)	2–28	13	100 T.U. O.T.	111	109 (98)
93a	11×10^6	10 T.U. O.T. 10 T.U. BCG(T) 100 T.U. O.T.	315	312 (99)	2–28	10	Jelly Heaf 100 T.U. O.T.	240	240 (100)
Commercially produced batches: Annual tests completed									
143	8×10^6	Jelly Heaf 100 T.U. O.T.	40	40 (100)	—	15	,,	35	35 (100)
132 142 162 166 190	$2{\cdot}4$–5×10^6	,,	789	785 (99·5)	3–20	6	,,	536	536 (100)
Annual tests not yet completed									
193 200 240 253 263 270	4–5×10^6	,,	274	274 (100)	2–15	6			
		Total						1,005	1,003 (99·8)

BCG (T) = BCG Tuberculin (Lorber, 1957)

Present Study

The purpose of this paper is to report on the efficiency of this commercially available freeze-dried B.C.G. and to extend our previous observations by reporting on the follow-up of children who were re-examined one year after vaccination. Altogether 1,103 children (mostly contacts) had completed the vaccination procedure after the completion of our previous trials. These were all vaccinated with commercially available batches. In addition we recalled for examination and tuberculin tested 1,005 children one year after their vaccination. Of these, 434 were vaccinated earlier with experimental batches of widely differing viability counts ($0{\cdot}1 \times 10^6$ to 23×10^6 per ml.), and 571 with commercial batches of far more uniform viability counts ($2{\cdot}4 \times 10^6$ to $8{\cdot}0 \times 10^6$ per ml.) (see Table).

Vaccination and tuberculin testing technique. All subjects had been shown to be tuberculin negative a minimum of six weeks after exposure to tuberculous infection. They were then vaccinated with B.C.G. and were kept away from such exposure for a further period until tuberculin conversion was demonstrated six to eight weeks later. Freshly reconstituted vaccine, 0·1 ml. was injected intradermally at the level of the insertion of the left deltoid muscle.

The routine tuberculin testing consisted of the tuberculin jelly test, which was applied by the Health Visitors in the children's own home four days before they attended the clinic. This was carried out before vaccination and six to eight weeks after it. If the result was doubtful, or if for some reason the jelly test had not been performed, or if the result was negative after vaccination, the Heaf test was used and read 96 hours later. Those still negative were finally tested with 100 T.U. (Mantoux 1/100). The same procedure was used one year after vaccination.

The vaccination lesions. A small group of 40 children was vaccinated with a batch containing 8×10^6 viable organisms per ml. The lesions in these were unduly large, averaging 15 mm. in diameter and crusting frequently occurred. The remaining 1,063 children were vaccinated with batches containing $2{\cdot}4$-$5{\cdot}0 \times 10^6$ viable organisms per ml. The vaccination lesions in all these were very acceptable, with an average diameter of induration of 6 mm. No ulceration was seen in any and the regional lymph glands in the axilla did not become palpable. One year after vaccination there was only a shallow colourless depression.

Tuberculin tests. All but four of the 1,103 (99·6%) children vaccinated with these commercial

batches became tuberculin positive six to eight weeks after vaccination and only one in 10 of those who had a jelly test required a Heaf test to prove tuberculin conversion.

Of the 434 children who were vaccinated earlier with experimental batches, 432 (99·7%) were tuberculin positive a year after vaccination and the only two negative reactors have not been tested either with the Heaf test or with 100 T.U. intradermally. It is of great interest that 83 children who had been vaccinated with the weakest vaccine containing only $0{\cdot}14 \times 10^6$ viable organisms per ml., and whose post-vaccination conversion rate was only about 56%, all became tuberculin positive one year after vaccination.

Conclusion and Summary

Freeze-dried B.C.G. has been proved in the laboratory to be of uniform consistency with a viable bacterial count which, if kept in a cool place, persists unaltered in the dry state for a year or longer. It is safe and convenient to use. Suspensions, 0·1 ml., containing approximately $2{\cdot}5 \times 10^6$ organisms per ml. were injected intradermally into over 1,000 children. The result was a papule, averaging 6 mm. in diameter. There was neither ulceration nor enlargement of the regional lymph-nodes. Tuberculin conversion was demonstrated in virtually 100% six to eight weeks after vaccination and a positive tuberculin reaction was maintained for up to at least one year after vaccination. In the case of others who were vaccinated with weaker vaccines the proportion of positive reactors increased with time, indicating the probability that prolonged tuberculin sensitivity will be produced with the freeze-dried vaccine in current use.

It is a great pleasure to thank Dr. J. Ungar and Dr. P. W. Muggleton of Glaxo Laboratories Ltd. for their continued help with these investigations, for supplying us with the laboratory data and for providing the vaccines; the Chest Physicians of Sheffield for referring so many patients to us, Dr. Llywelyn Roberts, Medical Officer of Health, Miss I. Littlewood, Superintendent Health Visitor, and her staff of the City of Sheffield, for their assistance, Professor R. S. Illingworth for his criticism and the Tuberculosis Research Fund of the University of Sheffield for a research grant to one of us (P.C.M.).

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A CASE OF OSTEOPETROSIS (ALBERS-SCHÖNBERG) WITH INTERCURRENT PNEUMOCYSTIS PNEUMONITIS

BY

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Albers-Schönberg (1904, 1907) defined the clinical and radiological features of a sclerosing disease of bone for which Karshner (1926) suggested the term osteopetrosis. As published cases of the disease accumulated, two types came to be distinguished (McCune and Bradley, 1934; Harnapp, 1937; Nussey, 1938; Zetterström, 1958). The first, or clinically 'malignant' type may be characterized by a refractory and often leucoerythroblastic anaemia, enlargement of liver, spleen and lymph nodes, a liability to multiple fractures, and death in infancy or early childhood. In the second or clinically 'benign' type, more commonly seen in adults, anaemia is mild and the osteosclerosis, though often severe, may yet be symptomless.

In the more severe forms of osteopetrosis, intercurrent infection, particularly of the respiratory tract, is a serious hazard. The case to be reported here, an example of the 'malignant' type, succumbed to an interstitial 'plasma cell' pneumonitis.

Though this unusual pneumonitis has been recognized for many years in central Europe its aetiology had been obscure until 1951. In that year Vaněk, in Czechoslovakia, identified *Pneumocystis carinii* in the lungs of all of a series of 16 fatal cases of this disease. In a series of papers (Vaněk, 1951; Vaněk and Jírovec, 1952; Vaněk, Jírovec and Lukeš, 1953) evidence was presented that *Pneumocystis carinii* was the causal agent of interstitial plasma cell pneumonitis. Nevertheless, Deamer and Zollinger (1953), who first drew American attention to the disease, concluded that it was probably a viral one; they dismissed a fungal or protozoal agent as unlikely. Baar (1955) reported the first case to be observed in England and subscribed to the hypothesis that *Pneumocystis carinii* was the pathogen. The subject is comprehensively reviewed by Gajdusek (1957).

Pneumocystis carinii pneumonitis has been found associated with congenital agammaglobulinaemia (Hutchison, 1955; Bird and Thomson, 1957; Russell, 1959), cytomegalic inclusion disease (Baar, 1955; Hamperl, 1956), and neoplastic disease of the lympho-reticular tissue in both children and adults (Vaněk, 1952; Jírovec and Vaněk, 1954; Le Tan Vinh, 1954; Hamperl, 1956). Association with Albers-Schönberg's osteopetrosis has apparently not been reported before.

Case Report

W.T. (Reg. No. R.I. 250922), was a male infant, the first-born and only child of healthy unrelated parents. Pregnancy and labour had been uneventful. In the first 24 hours bruises were noticed on his upper lip and on several toes. These bruises disappeared within a few days. On the second day he regurgitated blood-flecked milk. Nothing further happened until the 13th day when another bruise appeared on his right leg and a small haematoma-like swelling was found on his umbilicus. As these subsided others appeared near the anus and over the chest wall. He became progressively paler.

On admission to hospital at 3 weeks of age, he was pale but reasonably vigorous and not acutely ill. He weighed 5 lb. 14 oz. There were bruises on the left chest, right thigh, right groin and umbilicus. A small abscess cavity was found close to the anus posteriorly. The liver was palpated about a finger breadth below the costal margin, and though the spleen was not palpable at first it could be tipped after four days and readily palpated within a week. Apart from these there were no unusual clinical findings.

Laboratory Investigations on Admission. Hb 45% (6·6 g./100 ml.); erythrocytes showed some anisocytosis and poikilocytosis; there were no Heinz bodies. Leucocytes 34,000/c.mm. (blast cells 340, promyelocytes 700, myelocytes 1,400, band forms 2,700, segmented neutrophils 12,000, eosinophils 700, monocytes 3,400, lymphocytes 13,000); reticulocytes 1·0%; normoblasts (occasionally in mitosis) 5/100 leucocytes. There was, therefore, a severe leucoerythroblastic anaemia (Fig. 1). In addition, the platelet count (Lempert) gave 21,000/c.mm. (a proportion of which were abnormal giant forms) and the bleeding time (Ivy) was prolonged to 13 minutes. Clotting time (Dale and Laidlaw) was normal at 1 min. 50 sec. and the

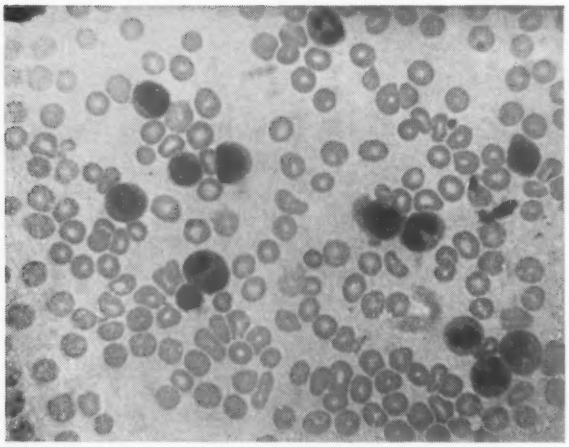

FIG. 1.—Peripheral blood film showing immature erythroid and myeloid cells. May-Gruenwald-Giemsa × 584.

tourniquet test was negative. The blood group was O Rh positive. The direct Coombs test was negative and the mother's serum was found to be compatible with the patient's erythrocytes. No platelet agglutinins could be demonstrated in the mother's serum. The toxoplasma dye test dilution was 1/6 and the toxoplasma complement fixation test was negative. Wassermann and Kahn reactions were negative in both mother and infant. Puncture of the tibial marrow was attempted unsuccessfully.

Progress in Hospital. Towards the end of the first week in hospital the perineal abscess was evacuated. A scalp vein transfusion of 110 ml. of blood brought the Hb level to 96% (14·2 g./100 ml.). After this there was some clinical improvement, but within 17 days the Hb had fallen again to 58% (8·6 g./100 ml.), i.e. at the rate of about 2·6% (0·3 g./100 ml.) daily although there was no haemorrhage during this period. The fluctuations in the haemoglobin levels are shown in Fig. 2 in relation to blood transfusion and blood loss. Serial leucocyte and platelet levels are shown in the Table.

Further scalp-vein transfusion of 100 ml. of blood restored the Hb to 96% (14·2 g./100 ml.). Five days later he developed epistaxis and began to ooze blood from the gums. About this time it was observed that any skin punctures tended to bleed excessively. During the next three weeks the Hb fell steadily to 46% (6·8 g./100 ml.) necessitating blood transfusion once again. A transfusion of 150 ml. was therefore given by an

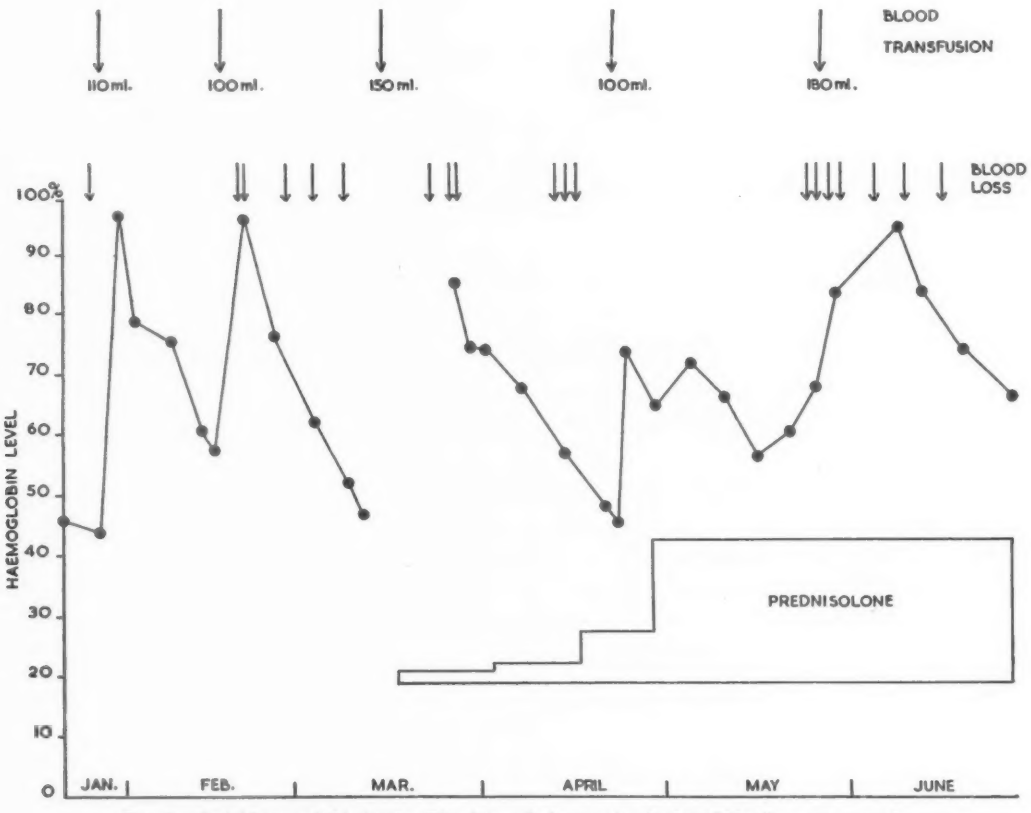

FIG. 2.—Serial haemoglobin levels. Blood transfusions and episodes of bleeding are arrowed.

TABLE

SERIAL LEUCOCYTE AND PLATELET LEVELS

Date	Treatment	Hb (%)	Reticulocytes (%)	Normoblasts/c.mm.	Platelets/c.mm.	W.B.C./c.mm.	Remarks
Jan. 23		45	1·0	1,700	21,000	34,000	
Jan. 28	Blood transfusion 110 ml.	43	2·2	5,800	20,000	64,500	
Jan. 31		96	—	1,300	67,000	66,000	
Feb. 5		76	—	1,000	61,000	48,000	
Feb. 10		75	—	280	48,000	28,000	Leukaemoid picture with about 1% blast cells; 2% promyelocytes; 5% myelocytes
Feb. 14		60	—	—	102,000	40,000	
Feb. 17		58	—	—	—	—	
Feb. 19	Blood transfusion 100 ml.						
Feb. 21		96	—	380	25,000	38,000	
Mar. 4		62	—	310	14,000	31,000	
Mar. 10		52	—	—	45,000	50,000	
Mar. 13		46	2·2	360	51,000	36,000	
Mar. 15	Blood transfusion 150 ml.						
Mar. 18	Prednisolone 1 mg. twice daily ..						
Mar. 28		84	—	—	50,000	28,500	
April 3	Prednisolone 1 mg three times daily	74	—	—	102,000	36,000	
April 15		56	—	2,850	91,000	57,000	
April 17	Prednisolone 2 mg. three times daily						
April 22		48	—	—	124,000	57,000	Disappearance of blast cells and promyelocytes; neutrophil leucocytosis with 1-3% myelocytes and 20,000-30,000 lymphocytes/c.mm.
April 24	Blood transfusion 100 ml.						
April 25		74	—	2,940	145,000	98,000	
April 29	Prednisolone 4 mg. four times daily ..						
May 12		67	3·8	4,000	240,000	80,000	
May 23		62	—	880	190,000	22,000	
May 28	Blood transfusion 180 ml.						
May 31		84	—	—	130,000	28,000	
June 9		95					
June 13		84	10	1,800	+	45,000	
June 20		75		3,050	+	77,000	

antecubital vein. Meanwhile the spleen was noted to be enlarging gradually. Septic skin lesions on the head and on the left hand were treated with oral terramycin.

Towards the end of the second month in hospital it was decided to treat him with prednisolone, at first in a dose of 1 mg. twice daily, increasing over the next four weeks to a maximum of 4 mg. four times a day. With this his general condition improved considerably, although he continued to show purpuric lesions over the skin and abdomen. The platelet count began to rise shortly after administration of prednisolone and reached the normal level of 240,000/c.mm. during the subsequent eight weeks.

Nevertheless, episodes of bleeding continued. Ten days after the start of prednisolone treatment severe epistaxis began again and continued in bouts during the next three weeks. It was eventually controlled by intranasal adrenaline sprays. By this time Hb level had fallen to 48% (7·1 g./100 ml.), now at the rather slower rate of 1·4% daily. A further blood transfusion of 00 ml. was given.

Marrow puncture was attempted again and yielded, ith some difficulty, a hypocellular but otherwise normal arrow. As a fortnight passed without blood loss, and e was in good general condition, he was discharged ome on 16 mg. of prednisolone daily.

While at home he caught a 'cold' and developed a ough. He went off his feeds, which he had been taking ell till then. He was therefore re-admitted, now the age of 4½ months. On examination his temperature as 99·6° F. and his breathing rate was 64 per minute. His colour was dusky and he looked ill. There was some nasal discharge and reddening of the fauces.

His breathing was grunting in character; the alae nasi were working and there was some intercostal recession. However, the percussion note and the breath sounds were normal and there were no adventitiae. The liver and spleen were still palpable but now smaller. A chest radiograph showed no definite radiological lesion.

Two days later there was a fresh crop of purpuric lesions on his abdomen, although his platelet count was now normal. He maintained a persistent low-grade fever with some cough but no physical signs in the chest. After a further transfusion of 180 ml. blood, which brought his Hb level from 62% (9·1 g./100 ml.) to 95% (14·1 g./100 ml.) his general condition improved though his breathing remained rapid and there was some further bleeding from nose and rectum. At this time the spleen had receded so that it could only be tipped. He was feeding well and seemed happy. He was discharged once again on prednisolone and oral erythromycin.

He was re-admitted five days later because his cough had become worse and he had gone off his feeds again. On examination he was pale and ill and had a weak cry. His breathing was still rapid though his chest appeared clinically and radiologically clear. The liver was palpable two or three finger breadths below the costal margin; the spleen could not be felt. He remained somewhat febrile, breathing at the rate of 60-120/min. On the 10th day of this admission he died suddenly at the age of 6 months.

Morbid Anatomy. At autopsy (P.M. 512/58) the following were the main macroscopical findings:

MACROSCOPICAL FINDINGS

Lungs. The lungs failed to retract as the chest was opened. Both were of a mottled café-au-lait colour. They presented a curious, vaguely nodular consolidation which was more marked in the lower lobes. The cut surfaces were dry and showed small scattered yellowish-white areas. The tracheobronchial tree was normal.

Liver. The liver (196 g.) appeared normal in size, consistency and colour.

Spleen and lymphoid tissue. The spleen (16 g.) was rather firm, but not appreciably enlarged. The cut surfaces appeared normal. Lymph nodes in general were inconspicuous. The thymus was involuted.

Bones. The calvarium appeared to be of average thickness and density. The features of the base of the skull were not detectably abnormal and the middle ears were opened without difficulty. Both femora were shorter than normal and very slightly clubbed. They proved very difficult to cut because of a dense sclerosis of the medullae. A vertebral body was similarly sclerosed. These excised bones and the remainder of the skeleton were radiographed and showed the following features: There was an overall increase in the density of the femur as compared with a normal control (Fig. 3).

FIG. 3.—Femur showing osteopetrosis compared with normal femur of similar age.

Trabecular detail was obscured and marrow spaces appeared small. Particularly dense transverse bands occupied the metaphyseal growth zone; that in the distal metaphysis of the femur measured more than 1 cm. in the axis of the bone. The distal epiphyseal centre of ossification was rather small and dense. Very similar changes were visible symmetrically in tibiae, fibulae, humeri, radii and ulnae. Clubbing was more obvious at the distal ends of the radii and the tibiae than elsewhere. Similar but slighter bands of metaphyseal density were visible in metacarpal bones. Pelvic bones, vertebrae, ribs, clavicles and scapulae showed some overall increase in density. In carpal, tarsal and skull bones the changes were too slight for dependable assessment.

HISTOLOGICAL FINDINGS

The Lungs. Both lungs showed an overall interstitial fibrosis. This was mainly due to an increase in reticulin but occasional collagen bundles contributed to it. The thickened alveolar walls and septa were infiltrated by mononuclear cells, some of which resembled plasma cells. Polymorphonuclear leucocytes were not seen in significant numbers. The alveoli and alveolar ducts in most areas contained an eosinophilic foamy material which was bordered in some alveoli by coalescing macrophages (Fig. 4). This material gave the tinctorial reactions of a polysaccharide (periodic acid-Schiff) through which small chromatin bodies (Giemsa: Feulgen) were distributed. It did not contain fibrin (Mallory's phototungstic acid-haematoxylin) or mucus (mucicarmine). Silver impregnation (Hortega) confirmed the presence of morphologically typical *Pneumocystis carinii* (Fig. 5). Viral studies were not made. The appearances were those of an interstitial pneumonitis in which the only detectable organism was the *Pneumocystis carinii.*

The Liver. The parenchymal cells contained rather large quantities of stainable iron.

The Spleen. The sinusoids were prominent and their littoral cells were plump. Many sinusoids contained large pale free macrophages. These phagocytes contained nuclei or fragments of nuclear material, a good deal of iron pigment and an occasional red cell ghost (Fig. 6). There was some excess of reticulin in the stroma. No evidence of haemopoiesis was found.

Lymph Nodes. These showed a fairly well marked excess of reticulin. Active haemopoiesis was visible in some nodes.

Bones. The disturbances affected endochondral ossification only mildly. Those seen in the femur will be taken as illustrative. *Mutatis mutandis*, similar changes were seen in other sites. The most striking feature was a massive persistence of calcified cartilage (the primary spongiosa) as irregular longitudinal islands, bordered and occasionally penetrated by immature new bone (Fig. 7). In the electron microscope the calcification of this cartilage was seen to be patchy but often unusually dense. The metaphyses were thus packed with stout anastomosing trabeculae of unresorbed primary elements and the enclosed marrow spaces were correspondingly small. This thicket extended in a modified form to the

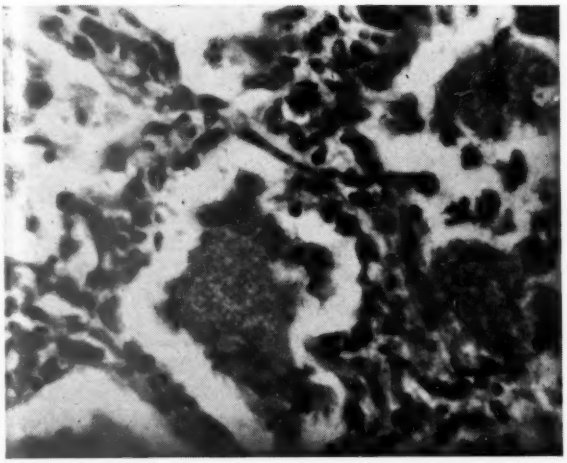

FIG. 4.—A group of pulmonary alveoli showing thickened alveolar walls and the foamy material of *Pneumocystis carinii*. H. and E. × 345.

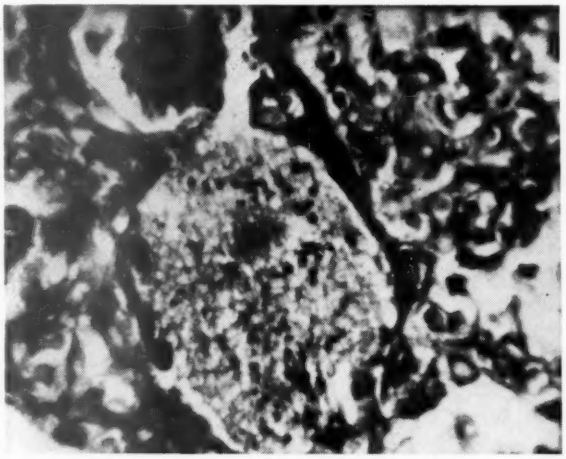

FIG. 5.—*Pneumocystis carinii* as demonstrated by silver impregnation. Hortega × 447.

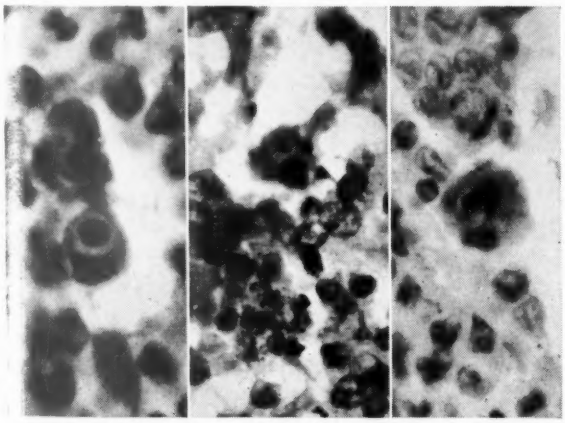

FIG. 6.—Composite picture of three splenic fields showing phagocytosis of a nucleated cell, an erythrocyte and some cell debris. H. and E. × 620.

diaphysis. Here spongy bone was still excessive but the cartilaginous component was diminished and the marrow spaces were considerably larger. In polarized light much of the new bone bordering the persistent cartilage showed normal lamellation. On the other hand the bone which had formed within vacated cartilage cell capsules showed no orientation of its collagen fibres. Both varieties of new bone were Schiff-positive.

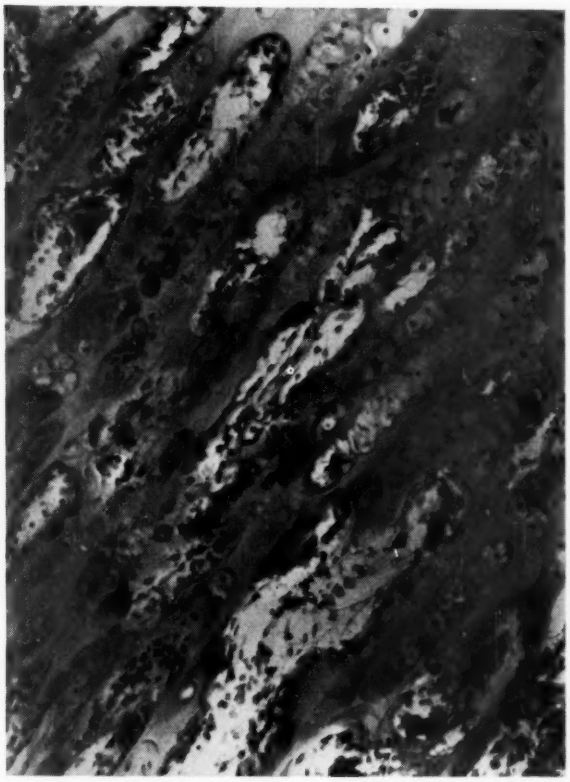

FIG. 7.—Metaphyseal growth zone of femur, showing abnormal persistence of cartilage and formation of dense chondro-osseous mosaic. H. and E. × 172.

Periosteal ossification was less disturbed but Haversian systems appeared poorly formed in many areas. Occasionally the cortex included some persistent cartilage and immature bone.

Bone Marrow. The small marrow spaces in the growth zone contained an excess of reticulin through which ran thick-walled capillaries. Normal bone similarly stained showed more delicate mesenchyme and larger thin-walled vessels in this region. The osteopetrotic metaphysis appeared less vascular than usual and the capillaries morphologically abnormal.

Haemopoietic tissue occupied the marrow spaces in the remainder of the bone. Erythropoiesis and leucopoiesis were both in progress and occasional megakaryocytes were seen. There appeared to be a mild hyperplasia of myelocytes, and colonies of these cells were especially noted along the adventitia of small

arterioles and along the borders of many trabeculae. Fat cells were very scanty. This marrow differed from normal marrow, similarly stained, in being more densely cellular and in not showing the usual prominence of marrow sinusoids. Where sinusoids could be discovered they contained both erythropoietic and leucopoietic cells, an appearance which suggested intravascular haemopoiesis.

Other Organs. Apart from some foci of calcium deposition in the medulla of the kidneys other organs were unremarkable.

Discussion

Generalized osteosclerosis in infancy may be secondary to congenital syphilis, heavy metal poisoning, excessive dosage with vitamin D and perhaps leukaemia. Of these diseases only leukaemia merits consideration in the present case. However, leukaemia typically causes osteolysis and on the rare occasions when it causes sclerosis this is found to be due to direct metaplasia of reticular or collagenous structures into woven bone (Windholz and Foster, 1949). Therefore this disease also may be ruled out.

Albers-Schönberg's osteopetrosis, on the other hand, accounts satisfactorily for both the clinical and the pathological findings. The clinical features closely resemble those of cases reported by Pines and Lederer (1947) and Turano, Fagan and Corbo (1954). The pathological structure of the bone is typical of osteopetrosis. As in previously reported cases the most obvious and probably the primary abnormality is a persistence of the calcified cartilaginous scaffolding upon which new bone is built. Layers of new Schiff-positive bone are seen on the surfaces of the cartilage masses, and tinctorially similar bone appears in the spaces from which cartilage cells have vanished. Normally a provisional design of this sort undergoes considerable modification. Most spongy bone and all remnants of cartilage are resorbed from the marrow cavity and increasingly lamellated bone is incorporated peripherally into the cortex. The appearances in the present case may be interpreted as the effect of a retarded remodelling process. Relatively little lamellar bone is present. Islands of immature bone, of which the collagen is unorientated, form a mosaic with the persistent irregularly calcified cartilage. The tensile strength of such tissue must be well below normal in spite of its apparent solidity.

Either the cartilage matrix is unusually resistant to remodelling or the mechanism of remodelling is defective. Of course, both factors may cooperate, but there is no evidence at present of abnormal cartilage matrix. On the other hand the vascular metaphyseal mesenchyme, which plays a major part in resorptive modelling, may well be at fault. Evidence in favour of this thesis may be found in the experimental work of Trueta and Amato (1960). They found that interruption of the blood supply to the metaphysis of growing bone inhibited the resorption of chondro-osseous tissue and delayed the formation of final bone. Large zones of calcified cartilage and preliminary bone remained at a level in the metaphysis where, normally, remodelling is taking place.

Many authors (McCune and Bradley, 1934; Lamb and Jackson, 1938; Clifton, Frank and Freeman, 1938; Pines and Lederer, 1947) have adopted Klemperer's (1931) suggestion that the fundamental disturbance in Albers-Schönberg's disease may lie in the undifferentiated mesenchymal anlage, the common progenitor of bone and marrow. Osteogenesis and haemopoiesis, according to this hypothesis, are both blighted by a prior defect involving mainly the former process in benign cases and the latter in malignant. But in the present case histological study did not suggest an intrinsic defect of osteogenesis. Similarly, Zetterström's (1958) biophysical studies led him to the conclusion that osteopetrotic bone comprises all those types of skeletal tissue which appear during the normal development of bone, the abnormality being a failure of normal removal. Furthermore, Pines and Lederer (1947) noted that the skeleton in general was poorly vascularized but that bone and marrow approached normal at sites of enhanced vascularity. In the present case also an impression of poor skeletal vascularity and of abnormal vessel structure was gained. The hypothesis of mesenchymal perversion might therefore be restated in a form which postulates abnormal vasoformation rather than abnormal osteogenesis. This view would suppose a mesenchymal defect which may involve predominantly the vascular remodelling tissue in benign osteopetrosis or the closely allied haemopoietic tissue in malignant osteopetrosis.

As in the cases of Lamb and Jackson (1938), Kramer and Halpert (1939), and others, the refractory anaemia could certainly not have been due to a simple crowding out of otherwise healthy haemopoietic tissue, as is commonly supposed to happen. In the present case the volume of the marrow cavity was estimated and found to be fully 70% of normal. Moreover, the marrow tissue was a good deal more cellular than normal. Therefore a merely mechanical theory of dyshaemopoiesis is plainly inadequate.

Though one may hypothetically attribute the leucoerythroblastic anaemia to a dysplasia of

narrow tissue other mechanisms must also be evaluated. Skin sepsis and episodic haemorrhage must have played their parts, though the haemoglobin level continued to fall on occasions when neither was operative. Red cell destruction probably played a major part. Zetterström (1958), using a radioactive chromium technique, found a mean red cell survival time of 35-40 days in one of his cases, a patient aged 10 years. With colleagues (Engfeldt, Karlberg and Zetterström, 1955) he found a shortened survival time of both native and donor cells in another patient aged 6 years, though this observation was not expressed quantitatively. He therefore suggested that the anaemia may be due to hypersplenism. Loeb, Moore and Dubach (1953) have found this to be true of certain cases of myelosclerosis; in these, splenectomy restored a shortened red cell survival time to normal. Sjölin (1959) reported four cases of malignant osteopetrosis in each of which accelerated red cell destruction was proved isotopically. Splenectomy improved the haemoglobin level in all cases, though the red cell survival time was not always restored permanently to normal. The platelet count, which had been low in all four cases, returned to normal and reticulocytosis diminished. The author concluded that hypersplenism was an important feature of malignant osteopetrosis.

Though no direct estimate of red cell survival was made in the present case the concept of hypersplenism is apposite. Admittedly a cellular marrow is not necessarily a productive one but the abundance of maturing cells, together with the presence of normoblasts in the peripheral blood and a continuous reticulocytosis, suggest that the anaemia was not wholly due to a failure of production. Furthermore, the steep fall of haemoglobin level (2·6% daily before administration of prednisolone), the marked haemosiderosis of liver and spleen (partly due to transfusion, no doubt) and the apparently enhanced activity of splenic phagocytes suggest excessive destruction.

The leukaemoid reaction is commonly supposed to be an expression of extramedullary haemopoiesis, at least in part; immature cells escape into the blood stream more easily from ectopic sites in soft organs. But the extent of haemopoiesis in the tissues at autopsy was surprisingly slight, as in many previously reported cases (Reiche, 1929, quoted by McCune and Bradley, 1931; Pease, DeSanctis and Falter, 1931; Lamb and Jackson, 1938). An alternative cause may lie again in dysfunction of the bone marrow itself, for which the observed myelocytic hyperplasia and the apparently intrasinusoidal haemopoiesis afford some evidence.

The tendency to haemorrhage is not completely explicable by thrombocytopenia and may have had a thrombasthenic component. Siegel, Friedman and Schwartz (1957) reported a patient with osteogenesis imperfecta tarda and an associated haemorrhagic diathesis due to increased capillary fragility and abnormal platelet function. These authors believed that their case represented a congenital defect involving two tissues of mesenchymal origin, the osseous system and the platelets. In the present case morphologically abnormal (giant) platelets were present and the haemorrhagic tendency persisted after the total platelet count had returned to normal.

Treatment with prednisolone brought about some improvement in the child's general condition and appeared both to decelerate the fall of haemoglobin level and to correct the leukaemoid state. The sclerosing process in the skeleton, on the other hand, was not abated. This is surprising, in view of the experimental findings of Baker and Ingle (1948) that 11-oxysteroids inhibited the proliferation of cartilage cells and brought about a profound and general atrophy of osteoblasts, so that the resorbtion of metaphyseal trabeculae occurred more rapidly than their formation. One might have expected prednisolone to be the rational treatment of osteopetrosis.

Prednisolone may have predisposed to infection with *Pneumocystis carinii* by further depression of a naturally low resistance. The result was the development of an interstitial pneumonitis of a type usually found in premature weakly infants or complicating diseases of the lymphoreticular system. It is of interest, furthermore, that prior and current treatment with prednisolone did not inhibit the development of a marked interstitial pulmonary fibrosis.

Summary

A case of 'malignant' osteopetrosis is reported. The patient presented in the neonatal period suffering from a leuco-erythroblastic anaemia complicated by a haemorrhagic tendency, and died at the age of 6 months primarily of an interstitial pneumonitis due to *Pneumocystis carinii*. An attempt is made to illustrate some of the problematical features of osteopetrosis. Future research might be directed towards studying the vascularity of the bone, evaluating the respective roles of dyshaemopoiesis and increased red cell destruction, and determining the adequacy of platelet function.

My thanks are due to Dr. Victoria Smallpeice for permission to publish this case, to Dr. A. H. T. Robb-Smith and Professor J. Trueta for critical advice, to many colleagues for their stimulating views, and to

Mrs. D. Jackson and Mr. E. L. Tugwell for the photographs.

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INTRAUTERINE BLOOD TRANSFER BETWEEN UNIOVULAR TWINS

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The non-haemolytic anaemias of the newborn have recently attracted the attention of many investigators. Of particular interest has been the anaemia due to occult blood loss of the foetus into the maternal circulation (Wiener, 1948; Chown, 1954; Gunson, 1957.

Another type of intrauterine occult blood loss has been recognized in the last few years as being due to transfusion of blood from one uniovular twin to the other through anastomotic vessels in the placenta (Herlitz, 1942; Bosma, 1954; Klingberg, Jones, Allan and Dempsey, 1955; Bergstedt, 1957; Betke, Deibel and Schlicht, 1958; Sacks, 1959). The present paper describes a similar case and our attempts to rectify it.

Case Report

The mother, a multigravida, 29 years of age, gave birth eight weeks before term to twin girls, the first weighing 1,250 g. and the second 1,500 g. Both babies breathed and cried immediately after delivery. A striking difference in colour was noticed; the first twin (A) appeared flushed and red and the second (B) was pale without any other signs of anoxia or shock. Venous blood was examined six hours after birth and a marked difference in the Hb and R.B.C. content was found (twin A: Hb 27·8 g. per 100 ml., R.B.C. 9,000,000 per c.mm.; twin B: Hb 8·2 g. per 100 ml., R.B.C. 2,600,000 per c.mm.). As it became evident that there had been intrauterine transfusion of blood from twin B to twin A, we decided to correct this unequal share of Hb. Eight hours after birth polyvinyl exchange-transfusion catheters were introduced into the umbilical vein of the babies. The venous pressure was found at the same level of 6-8 cm. in both twins. Blood was withdrawn in amounts of 5 ml. from the plethoric twin and was immediately given to twin B. No anticoagulant was used, but each catheter, while not used, was filled with a solution of normal saline containing heparine (1,000 units to one litre). In all, 25 ml. of blood was removed from twin A and transfused into twin B. Both twins tolerated the procedure well and we could record no change in the venous pressure or cardiac rate. As this first transfer of blood was not sufficient to bring the haemoglobin values near enough to normal the procedure was repeated 31 hours after birth when a further 25 ml. of blood was transferred from twin A to twin B. Full haematological details are recorded in Table 1.

The clinical condition of both babies continued to be good until the fifth day when twin A developed bronchopneumonia and died two days later in spite of treatment with antibiotics. At necropsy the diagnosis of bronchopneumonia was confirmed. The other twin continued to thrive and develop normally.

As soon as the diagnosis of intrauterine transfer of blood was made the placenta was examined. This was a single-ovum, monochorial, diamniotic placenta, weighing 680 g. One of the cords had a marginal insertion and its vessels spread over the larger part of the placenta. The insertion of the other cord was membranous and three of its vessels were found ruptured. By that time it was impossible to find out to which of the twins each cord belonged. A large yellow infarct measuring 5 × 6 cm. was seen in the periphery and between the two parts of the placenta. No difference in colour or fullness of the vessels between the two parts could be seen. The rupture of the cord vessels prevented us from performing a full 'milk test'. Nevertheless, neither by naked eye nor by injection of fluid through the other cord could we see a major anastomosis.

TABLE 1

BLOOD DATA OF THE TWINS

		Twin A	Twin B
Birth weight in grams		1,250	1,500
Colour at birth		Dark red	Very pale
Blood type		A, D	A, D
Venous blood at 6 hours	Hb g./100 ml.	27·8	8·27
	Haematocrit (%)	82	24
Blood from umbilical vein at 8 hours	Hb g./100 ml.	23·6	7·6
	Haematocrit (%)	74	22
	R.B.C.s per mm.³	7,900,000	2,600,000
	Reticulocytes (%)	6·5	18
	Erythroblasts per 100 W.B.C.	4	67
	Foetal Hb (%)	87·3	83·2
Venous blood at 22 hours	Hb g./100 ml.	21·9	10·7
	Haematocrit (%)	72	34
Venous blood 3rd day	Hb g./100 ml.	—	16·5
Venous blood 5th day	Hb g./100 ml.	18·67	—

TABLE 2

DATA FROM REPORTED CASES OF INTRAUTERINE BLOOD TRANSFER

Author	Sex of Twins	Order of Birth		Birth Weight (g.)		Initial Hb (g./100 ml.)		Icterus		Treatment		Outcome	
		A	B	A	B	A	B	A	B	A	B	A	B
Herlitz (1942) 1	M	II	I	2,580	1,580	160%	50%	None	None	None	Oral iron	A+W	A+W
Herlitz (1942) 2	F	I	II	3,030	2,220	200%	65%	None	None	None	Oral iron	A+W	A+W
Bosma (1954) ..	?	?	?	?	?	31	4	Marked	?	None	?	Kernik-terus	?
Klingberg *et al.* (1955)	F	I	II	2,690	1,770	25·2	3·7	Moderate (S.B.12·3)	None	Removal of 100 ml.	Exch. transf.	A+W	A+W
Bergstedt (1957) ..	F	I	II	3,030	1,810	23·6	13·6	Marked (S.B.23·5)	Slight	None	Oral iron	A+W	A+W
Betke *et al.* (1958)	M	I	II	2,600	2,130	24·6	9·5	Marked (S.B.22·4)	Slight (S.B. 7·1)	None	Trans-fusion iron, etc.	A+W	A+W
Sacks (1959) 1	M	II	I	2,084	1,431	24	5·5	Marked	None	Bleeding attempted	Trans-fusion	Kernik-terus	Cerebral palsy
Sacks (1959) 2	M	II	I	1,843	1,424	30	18	—	None	Removal of 60 ml.	Trans-fusion later	Died ate-lectasis	A+W
Sacks (1959) 3	F	I	II	2,523	2,041	33	12·8	Moderate (S.B.11·5)	None	Removal of 75 ml.	None	A+W	A+W
Sacks (1959) 4	F	II	I	1,163	1,021	27	15	—	—	—	—	Died at 16 hrs	Died at 26 hrs
Present case ..	F	I	II	1,250	1,500	27·8	8·27	Slight	None	Removal of 50 ml.	Trans-fusion	Died at 7 days	A+W

A = Polycythaemic twin. B = Anaemic twin.

Discussion

In the literature available to us we found 10 other pairs of twins exhibiting the same condition. Table 2 presents the relevant data from all the cases.

The present pair is the only one in which the polycythaemic twin was the smaller of the two. The unequal distribution of blood cannot be due, therefore, to the same cause as the unequal birth weight.

It is well known that there are numerous anastomoses of all types between the placental circulations of the identical twins (Schatz, 1898). The mere demonstration by the 'milk test' of the presence of these anastomoses constituting what is called 'third circulation' (Schatz, 1898) or 'parabiotic circulation' (Klingberg *et al.*, 1955) cannot explain the unequal distribution of blood. This could arise either during labour or exist for some time before. In our case the weight of evidence is in favour of the second alternative. There were no signs of oligaemia in the anaemic twin who, furthermore, showed marked erythropoietic activity. It seems, therefore, that the blood loss must have taken place sufficiently before labour to allow for the homeostatic mechanisms to reconstitute the blood volume and to stimulate the erythropoietic tissues. For the same reason blood loss through the ruptured vessels can be ruled out as the cause of the anaemia. Moreover, this explanation cannot account for the polycythaemia of the other twin.

Seip (1956) attributed the slightly higher haemoglobin values of the second-born observed in many pairs of twins to an additional amount of blood received from the placenta due to more complete uterine contractions. However, this explanation does not account for the great differences observed in the reported cases, in more than half of which, the polycythaemic twin was born first.

The mechanism of the unequal distribution of blood before the onset of labour is not clear. Klingberg *et al.* (1955) observed a difference in the colour and fullness of the vessels between the two parts of the placenta and believed that the more distended vessels belonged to the cord of the anaemic twin. They postulated some sort of obstruction in the venous return to the anaemic twin causing back pressure and a shunt of blood to the polycythaemic infant. We believe this to be a likely explanation but in our case we could not confirm this observation because of the rupture of the cord vessels.

Both twins are at risk but for a different reason. The anaemic infant begins its life with a low Hb content and previous authors (Klingberg *et al.*, 1955; Bergstedt, 1957; Sacks, 1959) gave blood transfusions for the correction of the anaemia. In the polycythaemic twin severe jaundice with its possible consequences is the main risk and in two cases (Bosma, 1954; Sacks, 1959) kernikterus occurred, while in two others (Bergstedt, 1957; Betke *et al.*, 1958) the serum bilirubin was above 20 mg. per 100 ml. It seems that the higher risk of kernikterus in polycythaemic newborn infants is due to the increased load of red cell breakdown

roducts presented to the liver cells for excretion. Klingberg *et al.* (1955) and Sacks (1959), with this risk in mind, removed blood from the polycythaemic twin.

In our case we avoided the danger facing each twin by returning to the anaemic infant the blood which was shunted to the polycythaemic before birth. Technically this procedure proved easy and it seems the best way to deal with such a situation.

Summary

A pair of uniovular twins one of which was anaemic and the other polycythaemic at birth are described. This difference was due to intrauterine transfusion of blood from one twin to the other.

The fault was corrected by removing blood from the polycythaemic twin and transfusing it to the anaemic.

We thank Professor N. Louros for permission to publish this case and Drs. M. Pavlatou and F. Fessas for help with the haematological investigations.

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Addendum

Another pair of uniovular male twins exhibiting the same condition was recently sent to us. Twin A weighing 2310 g. had Hb 23·3 g. and 7% reticulocytes. Twin B weighing 1670 g. had Hb 12·8 g. and 12% reticulocytes. When the infants were 14 hours old 40 ml. blood was taken from Twin A and given to twin B using the same technique as above; 24 hours later twin A had Hb 19·4 g. and of twin B 14·4 g. Twin A had slight jaundice never reaching dangerous levels.

PSEUDOHYPOPARATHYROIDISM IN INFANCY

BY

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(RECEIVED FOR PUBLICATION FEBRUARY 10, 1960)

Although many of the previously reported cases of this rare condition have occurred in childhood it has not previously been diagnosed during the first year of life, despite the fact that symptoms may begin in infancy (Peterman and Garvey, 1949; MacGregor and Whitehead, 1954; Cusmano, Baker and Finby, 1956). The following report records the youngest example of pseudohypoparathyroidism yet reported.

Case Report

M.M., a coloured male infant, was first investigated in the Paediatric Section, Coronation Hospital, at the age of 3 months, for convulsions which had commenced a week before admission. There was no history of birth trauma, neonatal jaundice or epilepsy in the family. Before the onset of the fits the child had been perfectly well. Until the age of 2 months he had been breast fed and this was followed by powdered whole cow's milk reconstituted to a dilution of three parts milk to one part water with added sucrose. Lumbar puncture, skull and chest radiographs, Wassermann reaction and serum electrolytes were all normal with the exception of the serum calcium which was found to be 3·0 mEq./l. (6 mg. %). The child was diagnosed as having hypocalcaemic tetany and discharged on a maintenance dose of vitamin D (shark liver oil) 3,000 units daily.

Three weeks following discharge the fits recurred and the infant was readmitted for investigation.

Examination revealed an underweight male infant weighing 7 lb. 8 oz. in a state of continuous tetany. There was pallor of the conjunctivae and mucus membranes. There was no evidence of nuchal rigidity and the head circumference was 14·5 in. Both Chvostek and Trousseau signs were strongly positive. Examination of the heart, lungs and abdomen revealed no abnormalities. Notable features were the short stubby fingers and toes and the round contour of the face.

The mother and grandmother of the child were both of markedly short stature (4 ft. 8 in.), but neither showed any abnormalities of the digits. There was one sibling, a girl aged 3 years, who was quite normal. Blood calcium and phosphorus estimations on the three subjects were within normal limits. No other member of the family was accessible for study.

Special Investigations. Radiographs of the skull, chest and long bones revealed gross demineralization of the entire skeleton. There was no evidence of intracranial or subcutaneous calcification.

Estimations on the blood revealed a mild hypochromic anaemia (Hb 9·6 g. %); the blood urea nitrogen was 38 mg. % and the serum sodium, potassium and chlorides were within normal limits. The Wassermann reaction was negative. Protein electrophoresis of the serum revealed no abnormalities. The urine contained neither albumin nor reducing substance. Microscopic examination of a centrifuged specimen revealed nothing of note. There was no excess of amino acids on chromatographic analysis. Estimations of the 24 hour excretion of both calcium and phosphorus were extremely low, the former varying between 9 and 12 mg. daily and the latter between 180 and 400 mg. daily. The *p*H of the urine was acid.

The serum calcium was 3·2 mEq./l. and the plasma phosphorus was 5·2 mg. %. The alkaline phosphatase was 23 King-Armstrong units.

Fat studies of the stools revealed no evidence of malabsorption.

Progress. After obtaining a baseline of blood calcium, phosphorus and alkaline phosphatase levels the patient was treated with 5,000 units of vitamin D daily with no improvement.

Several attempts were made to perform the Ellsworth-Howard test but these were frustrated by the inability to obtain suitable urine specimens. The patient was then given 100 units of parathormone (Lilly) every eight hours for four days with no significant rise in the serum calcium level. This particular batch of hormone had produced a phosphate diuresis in the control subject for the Ellsworth-Howard test.

Throughout the entire period of observation (Fig. 1) the serum calcium remained below normal and the patient was subject to repeated attacks of tetany until treated with dihydrotachysterol (AT10 Bayer) 3 ml. daily with added calcium supplements. Thereafter the serum calcium rose steadily to normal levels which were maintained. This was associated with a fall in the plasma phosphorus.

Discussion

The diagnosis in this case rests on the failure of parathyroid hormone administered parenterally to

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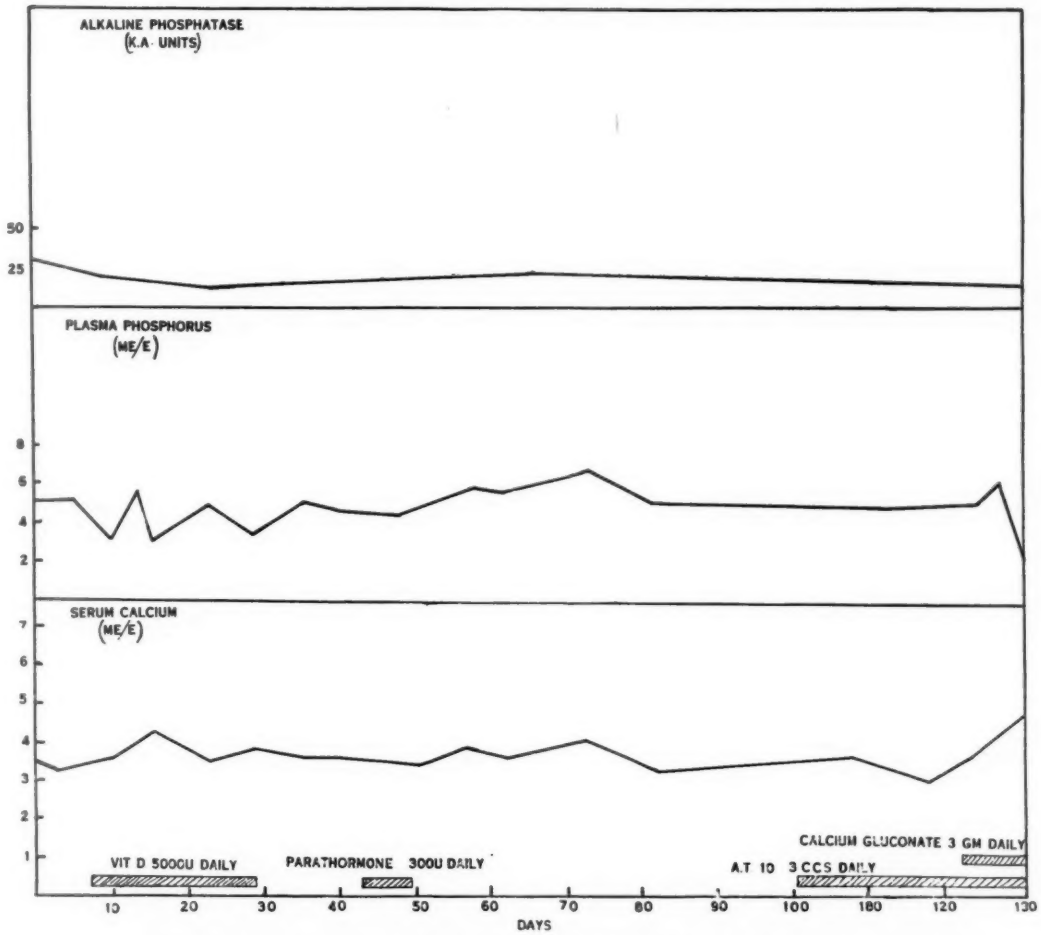

FIG. 1.—Serum calcium, plasma phosphorus and alkaline phosphatase levels and response to treatment.

produce a rise in the serum calcium with a concomitant fall in the phosphorus level. It was found impossible to collect the hourly specimens required for the Ellsworth-Howard test, the diagnostic procedure originally advocated by Albright, Burnett, Smith and Parson (1942). However, recently, workers have cast doubt on the validity of the procedure and suggest that the response of the serum calcium and phosphorus levels to parathyroid hormone over a definite period of time is a more reliable method of assessing tissue response to parathyroid (Dent, Bishop and de Mowbray, 1953; MacGregor and Whitehead, 1954; Wilkins, 1957). It is thus felt that the diagnosis in this case is valid in spite of the inability, for technical reasons, to demonstrate the classical absence of phosphorus diuresis.

Chief interest in this case lies in the youth of the patient. Many of the previously reported cases had undergone irreversible changes including cataracts, mental deficiency and subcutaneous and intracranial calcification. Our patient was quite free of these stigmata. It seems, at least, likely that some of these sequelae might be averted if cases were diagnosed early and effective treatment instituted before changes occurred.

Of considerable interest is the presence in this patient of skeletal decalcification. Eight similar cases have been collected from the literature and it appears likely that they form a definite entity. In many of this group, demineralization of the bones with symmetrical shortening of the metacarpals is the dominant radiographic finding (Peterman and Garvey, 1949; Elrick, Albright, Bartter, Forbes and Reeves, 1950; Reynolds, Jacobson, Edmondson, Martin and Nelson, 1952; MacGregor and Whitehead, 1954; Prentice, 1954; Frame and Carter, 1955; Oberst and Tompkins, 1955; Jackson, Hoffenberg, Linder and Irwin, 1956). This, together with the low serum calcium levels suggests that there is a

generalized depletion of the total body calcium which cannot be accounted for by the accepted theory that there is a failure of tissue response to parathyroid hormone. In addition, this depletion cannot be explained by the ectopic areas of calcification. It seems likely that there is, in addition to the failure of parathyroid response, either decreased absorption of calcium from the gastro-intestinal tract or excessive loss in the urine. It is known, however, that urinary loss of both calcium and phosphorus is extremely low in these cases. Furthermore, nephrolithiasis has not been described as a complication. One must conclude therefore that calcium absorption is impaired. It is also of interest that some cases of pseudo-hypoparathyroidism require additional calcium supplements as well as AT10 or massive doses of calciferol in order to raise the serum calcium to normal levels. The present patient shows this feature. Despite the fact that he was receiving three times the recommended adult dose, it was only when oral calcium gluconate was added to the regimen that the serum calcium responded. That this defect is not due to vitamin D deficiency is indicated by the raised plasma phosphorus in these cases and the normal alkaline phosphatase. It seems possible that there is, in these patients, a selective block to the absorption of calcium from the gastro-intestinal tract. It is suggested that this might take the form of an additional enzyme defect in the intestinal mucosa, resulting in the defective absorption of calcium. The exact nature and existence of this defect can only be elucidated by calcium balance studies.

Summary

Pseudohypoparathyroidism is described in a 4-month-old infant.

The presence of generalized decalcification of the skeleton is noted and eight similar cases collected from the literature.

It is suggested that in addition to the failure of tissue response to parathyroid hormone there is an additional enzyme defect present, manifesting as an impairment of absorption of calcium from the gastro-intestinal tract.

I wish to thank Dr. Harold Falcke and Dr. Harvey Cohen, Paediatricians at Coronation Hospital, and Dr. O. Elliot, Superintendent at Coronation Hospital, for permission to publish this case and the Photographic section, Department of Medicine, University of the Witwatersrand for the Figure.

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SUBSEROSAL HAEMATOMA OF THE ILEUM

BY

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Angiomas of the ileum are rare. Their association with a duplication cyst has not so far been described. The unusual mode of presentation, with intestinal obstruction and a palpable mass (subserosal haematoma) simulating intussusception, have prompted the report of the present case.

Case Report

N.C., a white male infant, born June 18, 1958, was admitted to hospital on May 18, 1959, when 11 months old, with a five days' history of being irritable and apparently suffering from severe colicky abdominal pain for the previous 24 hours. On the day of admission his bowels had not moved and he vomited several times.

He looked pale and ill and a mass could be felt in the right hypochondrium. There was no significant abdominal distension and the bowel sounds were within normal limits. A saline enema was given which showed a small amount of mucus but no blood. A diagnosis of intussusception was made, and after resuscitation with intravenous therapy the same evening laparotomy was performed, which showed no evidence of intussusception, but instead a large subserosal haematoma, involving approximately 7 cm. of ileum, 30 cm. from the ileo-caecal junction, and which formed the tumour that had been felt clinically (Figs. 1 and 2). In the middle of the haematoma there was a hard yellow small tumour; the mesenteric glands were slightly enlarged and some were blueish in colour. Resection of the diseased segment with end-to-end anastomosis was performed, and the appendix was removed.

The child remained ill for a few days but recovered and was discharged home on the seventh postoperative day, when he was taking feeds well and gaining weight.

When last seen, two months after operation, he was thriving and no further appointment was considered necessary.

The appendix, as expected, showed no macro- or microscopic abnormality; the mesenteric gland showed, on microscopic examination, only sinus catarrh. The resected gut, on macroscopic examination, showed a segment of intestine 9 cm. long, half way along which there was a haemorrhage over an area of 4 cm., which had lifted the serosa from the rest of the wall. On the outer aspect, also half way, there was a small diverticulum 1 cm. long, which, however, did not appear to communicate with the lumen of the small bowel. Opposite, the mucosa had a small erosion'.

Microscopical examination (Figs. 3, 4 and 5) showed that 'considerable haemorrhage had occurred in the serous, muscular and mucous coats. The mucosa, however, was viable and the maximal zone of damage was towards the serosa. Numerous large capillaries were present in the coats. The lining of the diverticulum formed by glandular epithelium suggesting ileal mucosa was partly destroyed, but it had a well-formed muscular coat': it was considered to be probably a duplication. The main diagnosis was that of haemangioma of the ileum.

FIG. 1.—Resected specimen showing subserosal haematoma and narrowing of the intestinal lumen as well as a small mucosal erosion at the level of the duplication.

FIG. 2.—Resected specimen showing duplication cyst.

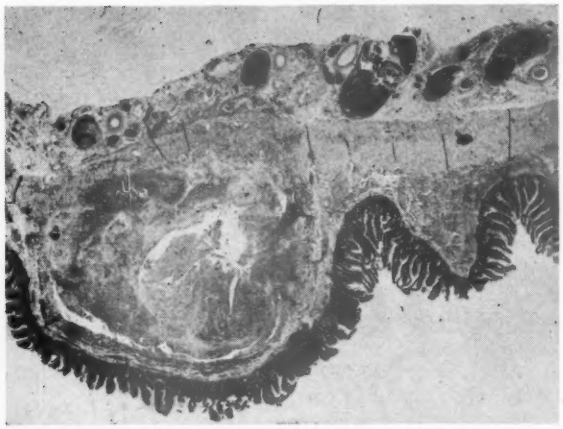

FIG. 3.—Low power magnification showing numerous vascular spaces in the subserosal area and a large area of haemorrhage in the submucosa.

FIG. 4.—Low power magnification of the duplication cyst and the common muscular wall with the intestine.

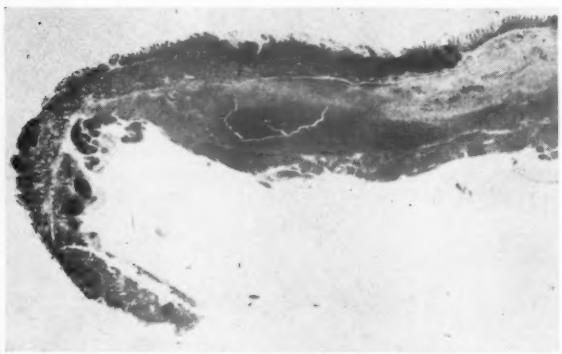

FIG. 5.—Lower power magnification in the main zone of haematoma formation, with haemorrhagic infiltration of all the bowel wall.

Discussion

As haemangiomas are common in children it is surprising to find how rarely they involve the gastro-intestinal tract. The great majority of cases have been reported in adult life. According to Hansen (1948) only 66 haemangiomas of the small bowel have been reported in the literature, and of these, only two were malignant (Ewing, 1940). Raiford (1932) quoted by Rickham (1952) found, in a series of 11,500 autopsies, that haemangiomas of the small bowel constituted 0·3% of all tumours of the gastro-intestinal tract.

They can be diffuse infiltrating lesions with resultant thickening of the wall and narrowing of the lumen, or localized tumours projecting into the lumen. They are sometimes multiple and may be associated with haemangiomas elsewhere.

Simple capillary and/or cavernous haemangioma of the small bowel present frequently with gastro-intestinal bleeding and occasionally are the leading point of an intussusception. More rarely they can lead to intestinal obstruction, due to the size of the tumour itself.

We think the case reported here is the first case described which presented by a subserosal haematoma. The differentiation from an intussusception was obviously impossible clinically. Treatment, however, was not influenced by the diagnosis as laparotomy was indicated in both cases.

Subserosal haematomas leading to intestinal obstruction have been reported by Zabin (1952), Lampert, Goodfellow and Wachowski (1954), and Robbarts (1957), but in those cases the children were older, with a definite history of non-penetrating abdominal injury, and examination of the resected specimens did not show haemangiomas. They were usually found near the more fixed zones of the gut, mainly near the duodenojejunal flexure.

The finding of a tumour in the centre of the area of haematoma made us look for some relationship between them, but without success. The tumour was small, smooth, rounded and yellowish, with a well-defined muscular wall in part common to the gut wall. It was cystic, with no communication with the intestinal lumen, and must be considered as a small duplication cyst. Although it is true to say that no agreed theory has so far been presented to explain the formation of those intestinal duplications, it seems certain that embryologically the haemangioma and the duplication have different origins and must be considered as coincidental but unrelated findings. Duplications of the gut, although not frequent, are a well known entity to the paediatric surgeon: Gross (1953) describes 71 cases, of which 19 were in the ileum. In the Alder Hey series Basu (1959) found seven in the ileum, out of a total of 29.

Although intramural haemorrhage in association with duplication of the intestine has been described

e could not find, in our case, evidence of the bleeding being due to the duplication.

The treatment of subserosal haematoma is section, particularly when associated with any other bowel lesion, e.g. tumour, duplication. In the traumatic cases also we favour resection and feel that the simple evacuation of the blood clot, although successfully used by Lampert *et al.* (1954) and Robbarts (1957) should only be employed in exceptional circumstances when resection is too risky or contra-indicated.

Summary

A case of haemangioma of the ileum in an 11-month-old boy, presenting with subserosal haematoma leading to marked narrowing of the lumen and to intestinal obstruction, and showing a clinical picture typical of intussusception, is reported.

A small duplication of the ileum was found at the same level and considered to be a coincidental but unrelated finding.

My thanks are due to Miss Isabella Forshall for allowing me to publish this case; to Drs. Edward G. Hall and Jean Bouton for the pathological report, and to Mr. Charles Fitzsimons for the microphotographs.

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A CASE OF WOOLLY HAIR NAEVUS

BY

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This rare anomaly of the hair was first described by Wise (1927) and since then has received little attention in dermatological textbooks and literature. Wise reported on 'a peculiar form of birth mark of the hair of the scalp, hitherto undescribed, with a report of two cases'. He named the condition woolly hair naevus.

The disorder occurred in two unrelated 5-year-old girls, both of whom had light woolly hair on one portion of the scalp while the rest of the hair was straight and brown. One had a linear naevus of the skin of the back of the neck, right elbow and wrist, on the same side as the woolly hair on the scalp. In advancing his reason for the designation given to the condition, Wise stated that birthmarks of the hair are changes in the 'colour, consistency, structure and morphology of the hair shaft'.

Wise and Sulzberger (1932) described a similar scalp anomaly in two cases of 'acquired progressive kinking of the scalp hair accompanied by changes in its pigmentation'. The patients were adult males with kinky black hair growing over the frontal, temporal and parietal areas of the scalp which progressed rapidly when it developed. The condition appeared in adult life and the hair became darker in contrast to Wise's earlier cases which were children and in which the hair was of a lighter colour than that of the remainder of the scalp.

There was a lapse of 16 years before any further reports appeared in the literature. Anderson (1943) presented a case to the Los Angeles Dermatological Society. The patient was a 5-year-old girl and the lesion had been present since birth and had been gradually increasing in size. The naevus was on the left side of the scalp and consisted of an irregular, oval area in which the hair was lighter and closely kinked. The scalp in the affected area was of a café au lait colour which extended down in a streak on the left side of the neck. In the discussion on the case it was stated that the condition was apparently a naevus of an unusual type, showing woolly hair quite different from the hair on the other parts of the scalp.

Sweitzer (1948) presented a case to the Minnesota Dermatological Society which he called woolly hair naevus. The case was that of a 4-year-old girl who had a scanty growth of hair with a fine kinky texture. In this case the hair had been shed at the age of 5½ months and replaced by a scanty down; there had been no further growth since the child was 2 years old. There was no evidence of any inflammation of the scalp nor was there any evidence of naevi elsewhere. In the discussion of this case it was stated that in the original cases the condition was characterized by localized areas of woolly hair among normal hair, while in this case it was a generalized condition. There was a suggestion of an ectodermal defect in the quality of hair and, therefore, it did not seem that this was a genuine example of woolly hair naevus.

Since these reports four other cases have been described. Hoffmann (1953) described a case in which there was a considerable amount of seborrhoea of the woolly hair portion of the scalp. This case, first seen at the age of 4 years in 1917, had areas of bright, thin, spiral crinkled hair. The microscopic appearance of the affected hair showed it to be thinner than normal, more flat and less pigmented. The medullary part was more or less missing. The skin of the affected areas was browner than the skin of the remainder of the scalp and its surface was somewhat rough. Nine years after first being seen the condition was unchanged but it appeared that the affected hairs grew more slowly than the normal hairs. Hoffmann (1953) called the condition crinkly hair naevus (*naevus ulotrichicus capillitii*) and stated that differentiation must be made between crinkly hair naevus and negro hair and familial curly hair which involves the whole scalp.

Knierer (1955) described a case which resembled the condition reported by Wise and Sulzberger (1932); the patient was an adult and the hair in the affected areas was darker than elsewhere. Born (1957) and Post (1958) also reported cases which resembled those originally described by Wise.

n Post's patient, a 7-year-old boy, the woolly reas were accompanied by linear verrucous naevi n the face, neck and arm. In none of the reported ases has there been a family history of a similar bnormality.

Until now it appears that this condition has not been described in British literature and the present case is the first to be reported upon in Britain so far as is known.

Case Report

A boy, aged 6 years, was seen at the out-patient department; for about four years his hair had shown a patchy fuzziness, which was now thought to be becoming more obvious. The boy's mother stated that he had been born with no hair on the scalp and it was not until he was 2 years old that he began to develop scalp hair, which was noticed to have a peculiar patchy and fuzzy appearance, the fuzzy areas being of a lighter colour than the rest of the scalp hair. The first area to be noticed was over the back of the head and, thereafter, further areas had appeared.

During the past four years the areas had extended slightly, had remained fuzzy, and had been persistently lighter in colour than the unaffected areas. At no time was it noticed that the abnormal hairs were deficient in growth nor did they appear to be any weaker than those of the rest of the scalp.

Family History. The patient's parents were alive and well and had no hair defects or other abnormalities. The patient was the younger of two children, the elder brother being healthy with no congenital defects. The patient was a normal full-time spontaneous delivery. His maternal uncle was said to have had some defect of his hair but this was thought to have been a generalized condition. No examination could be carried out as the uncle had been in Canada for five years and had apparently now lost most of his hair. It was not considered that he had had a woolly hair naevus.

Past History. The patient's general health was excellent. He had measles at the age of 4 years and had been known to suffer from myopia for about one year, having worn glasses since that time.

Examination. The general appearance was that of a normal healthy boy, with no abnormal findings on general examination. Examination of the scalp showed normal distribution of hair with no obvious deficiency of growth. There was no seborrhoea or other scalp abnormality. The most striking feature was the presence of areas of fuzzy, lustreless hair which were noticeably lighter in colour than the rest of the scalp hair. The normal hair was dark brown and the affected hair was a much lighter brown. The involved areas were over the occipito-parietal regions on both sides, the temporo-parietal regions on the right and left and the frontal aspects of the scalp. These areas were separated by the much darker areas of straight normal hair (Fig. 1) and the affected

FIG. 1.—Woolly hair naevus.

hairs, despite their appearance, were of the same texture as the rest of the scalp and showed no increased fragility. The eyebrows were of normal appearance and there was no abnormality of the finger and toe nails or the teeth. Examination of the eyes revealed a web-like opacity over the pupil of the right eye (Fig. 2).

He was referred to the ophthalmologist whose report was as follows: 'The patient has a very extensive moderately dense membrane covering the pupillary area of the right eye. It arises from the lesser circle and, as can be readily seen, it allows free movement of the pupil. There are fine openings in the membrane and it is un-

FIG. 2.—Persistent pupillary membrane.

likely that the vision in the eye is affected by it. No treatment is recommended.'

Microscopic examination of hairs from the affected and normal areas revealed no abnormality of the hairs. There was no evidence of monilethrix, trichorrhexis nodosa, pili torti, or other hair defects. The affected hairs were slightly curly and they were rather less pigmented than the normal straight ones.

Discussion

The case described is, in the writer's opinion, an example of the condition described by Wise as woolly hair naevus. There is, in common with all previously reported cases, no family history of similar naevoid changes in the scalp hair.

The diagnosis should be straightforward once the condition has been recognized. The differentiating points in distinguishing it from the condition described by Wise and Sulzberger (1932) are that it is not an acquired anomaly; it occurs in children; in all cases the affected areas are lighter in colour than the normal hair; it is not a generalized condition but a patchy one; the affected areas are interspersed by normal and darker hairs; it does not spread rapidly when it develops; and there is no microscopic abnormality of the affected hairs. Other hair abnormalities can be ruled out by the fact that in most of them there is a deficiency in hair growth and an increased fragility of the hairs which is not apparent in woolly hair naevus. Microscopic examination of the hairs will decide the diagnosis as other defects have a characteristic appearance.

Post (1958) suggested that there are three types of woolly hair naevus: (1) a type without any visible changes of the glabrous skin or scalp, (2) a type accompanied by linear naevi of the skin and (3) a type acquired in adult life in which the hair of the scalp assumes the characteristics of the pubic hair. While accepting the first two groups, the case under discussion being an example of the first, the writer feels that the third group should not be classified as a woolly hair naevus but should be classified as acquired progressive kinking of the hair as described by Wise and Sulzberger (1932).

The persistent pupillary membrane is not so rare a condition as it was once thought to be and has been reported as being found in 506 out of 1,600 eyes. It is most common in infants and children, and rare in old age as it tends to be absorbed with advancing years. Pupillary membrane remnants have the essential characteristic that if they retain contact with the iris they are always attached to the superficial mesodermal layer on its anterior surface usually at the lesser circle or occasionally more peripherally. In all cases they are extensile and do not impede movements of the pupil or interfere with vision unless they are very dense. As regards the present case, it is felt that the presence of a mesodermal defect associated with an ectodermal one is purely coincidental and of no special significance.

Summary

The literature on woolly hair naevus is briefly reviewed and a case is described which had no associated skin or scalp changes. The patient had a persistent pupillary membrane. As far as is known, no similar case has previously been reported in Britain and this is only the seventh example so far described in world literature.

I would like to thank Dr. A. Girdwood Fergusson for his helpful criticism and for permission to publish this case, Dr. A. M. Brogan for the ophthalmic report, and Mr. P. S. Waldie for the photographs.

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CAROTID THROMBOSIS IN CHILDHOOD

BY

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Although carotid occlusive disease is not uncommon in adults (Fisher, 1954; Samuel, 1956), it is rare in children. Since atherosclerosis is accepted by most authors as the major aetiological agent, this is not surprising. A search of the literature reveals 16 cases of carotid occlusion in persons 10 years of age or less (Duffy, Portnoy, Mauro and Wehrle, 1957; Cabieses and Saldias, 1956; Behrman, 1954; Shapiro, 1952; King and Langworthy, 1941; Litchfield, 1938; Gross, 1945; Martin, Lukeman, Ranson and Geppert, 1954; Goldstein and Burgess, 1958; Pouyanne, Arné, Loiseau and Mouton, 1957; Clark and Linell, 1954; Braudo, 1956; Fairburn, 1957) and a further six below the age of 20 (Pouyanne *et al.*, 1957; Krayenbühl and Weber, 1944; Petit-Dutaillis, Janet, Thiébaut and Guillaumat, 1949; Riechert, 1938; Caldwell, 1936).

Arteriographic, necropsy or operative proof was provided in 17 of these cases; two were diagnosed on the absence of carotid pulsation on the side opposite the hemiplegia and three, associated with trauma, were accepted on convincing circumstantial grounds.

An aetiology was indicated in 13 cases. Litchfield (1938) and Pouyanne *et al.* (1957) have each reported a case associated with severe throat infection. Gross (1945), in a review of arterial occlusion in infancy, reported two cases in whom emboli from a thrombosed persistent ductus arteriosus were considered to have caused the occlusion. One of these cases also had Fallot's tetralogy with polycythaemia. A paradoxical embolus of necrotic placental tissue was presumed by Clark and Linell (1954) to have caused internal carotid occlusion in an infant with erythroblastosis foetalis. In the case reported by Duffy *et al.* (1957) thrombosis was probably due to a congenital anomaly of the vessel wall. Martin *et al.* (1954) have described a case of mucormycosis of the central nervous system in which the thrombosed internal carotid artery was heavily invaded by the organism. Riechert's case (1938) appears to have been related to the presence of a nearby intracranial tumour. Trauma accounted for five cases (Braudo, 1956; Fairburn, 1957; Caldwell, 1936), direct injury to the soft palate being responsible in each instance.

In all of the proven cases the occlusion was limited to one or other internal carotid artery; one of the others (King and Langworthy, 1941) was thought to have common carotid and right subclavian obstruction on clinical grounds. Bilateral carotid involvement is occasionally encountered (Ochs, Sensenbach and Madison, 1954; Batley, 1955; Silverstein, 1959; Brain, 1957), but has never previously been reported in a child. Common carotid thrombosis constitutes a small fraction of several series of carotid occlusive cases (Silverstein, 1959; Shapiro and Peyton, 1954; Ameli and Ashby, 1949; Gurdjian and Webster, 1953) but no proven case in childhood has yet been reported. The following case of a child with bilateral common carotid thrombosis may thus be worth reporting.

Case Report

A girl of 2¼ years, was admitted to the Royal Liverpool Children's Hospital for investigation, having recently recovered from an illness diagnosed as left ventricular failure associated with respiratory infection. She was known to have a precordial systolic murmur since the age of 2 months when she presented with a chest infection.

On admission there was no evidence of congestive failure and she was not dyspnoeic. Sinus rhythm was present. The left radial and femoral pulses were diminished and delayed compared with the right radial, and blood pressures were as follows: right brachial 180/130 mm. Hg, left brachial 135/85 mm. Hg, right femoral 110/90 mm. Hg. Both carotid pulses were palpable and of high tension. Scapular collateral arteries could be felt only on the right. The toes were moderately cyanosed but the fingers only slightly. The heart apex beat gave the powerful localized thrust indicative of left ventricular hypertrophy and on auscultation a short systolic bruit of slight to moderate intensity and a short mid-diastolic bruit of moderate intensity were present at the apex. The second heart sound was somewhat accentuated and single. The clinical state was otherwise within normal limits.

The chest radiograph showed a cardio-thoracic ratio

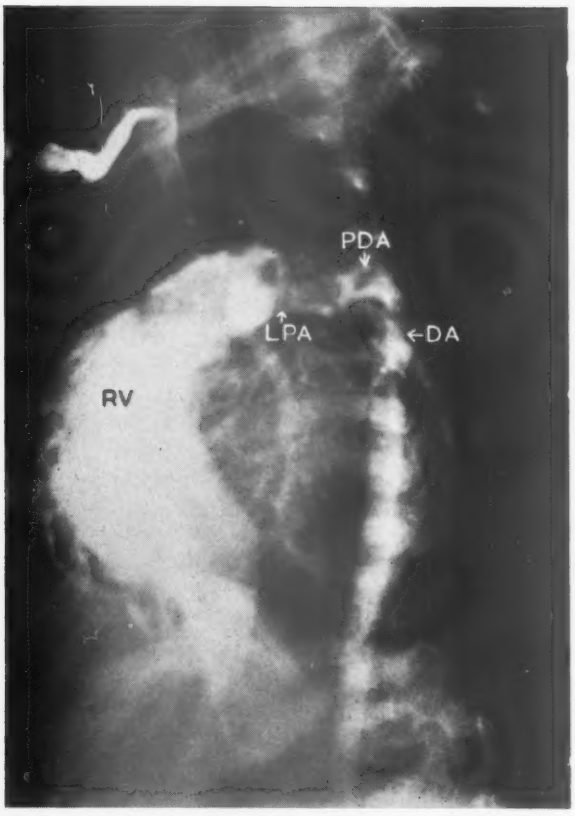

FIG. 1.—Angiocardiogram taken in right posterior oblique position, showing direct passage of dye from left pulmonary artery to descending aorta via ductus arteriosus.
RV = right ventricle; LPA = left pulmonary artery; PDA = patent ductus arteriosus; DA = descending aorta.

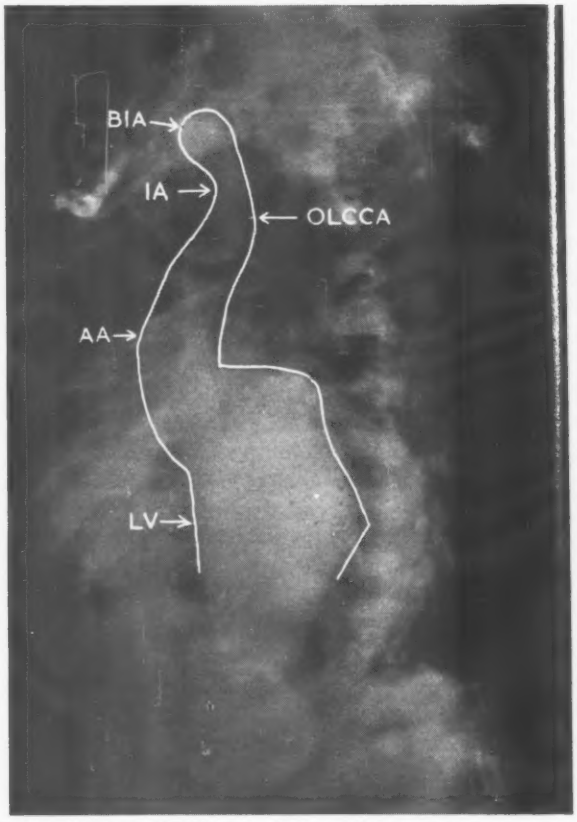

FIG. 2.—Angiocardiogram at a later stage than that shown in Fig. 1. That portion of the dye which has passed through the pulmonary circulation outlines only the left ventricle, the ascending aorta and the innominate artery. Neither carotid vessel has filled. Reference to Fig. 3 assists orientation.
LV = left ventricle; AA = ascending aorta; IA = innominate artery; BIA = region of bifurcation of innominate artery; OLCCA = region of origin of left common carotid artery.

of 0·69 and the pulmonary vascular markings were heavy. The electrocardiogram was interpreted as showing biventricular hypertrophy. Her haemoglobin was 95%, white cell count 13,000/c.mm., differential count normal, urine normal and blood urea 25 mg./100 ml.

Two weeks after admission the patient suddenly developed left hemiparesis; this improved considerably within a few days. She had always been irritable and after this episode her temperament worsened. It was not until two weeks later that the carotid pulses were checked when neither could be felt at all.

Angiocardiography was carried out and this showed direct filling of the descending aorta from the pulmonary artery via a patent ductus arteriosus (Fig. 1). The small proportion of dye which passed through the lungs outlined only the ascending aorta and innominate artery (Fig. 2).

Three days later the right hand and forearm suddenly became cold and blue. The right brachial pulse was unaltered but the radial and ulnar pulses had disappeared. Heparin and 'Priscol' were administered and after several days the colour and temperature of the limb improved. The pulses remained unchanged. A week after the onset of this episode the patient suddenly became unconscious and died a few hours later.

At autopsy (see Fig. 3) the heart was found to be greatly enlarged. The right ventricle was well developed and its wall up to 5 mm. thick. The left ventricle was markedly hypertrophied, its wall being up to 15 mm. thick and its endocardium white and slightly thickened. The pulmonary artery was normal in appearance but larger in size than the ascending aorta. The ductus was patent and 5 mm. in diameter. There was marked constriction of the aortic arch between the origins of the left common carotid and left subclavian arteries, admitting only a very fine probe. The left atrium was essentially normal apart from some whitening of the endocardium and slight thickening of the mitral valve cusps. The right atrium and the other three valves were normal and there was no abnormality in the anatomy of the pulmonary or systemic venous connections. Atrial and ventricular septa were intact. Adventitial haemorrhages were visible in the following sites: (*a*) over the root of the left common carotid artery where it was joined by the

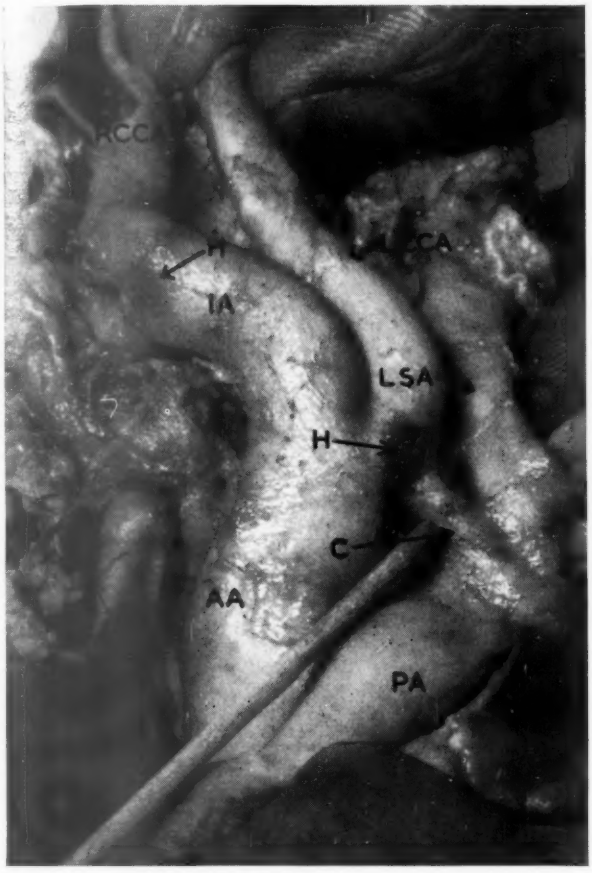

FIG. 3.—Great vessels. The right common carotid artery has been opened at its bifurcation to show the presence of thrombus. A haemorrhage can be seen in the wall of the left common carotid vessel at its junction with the coarctation; another at the bifurcation of the innominate artery is less well seen.
AA = ascending aorta; IA = innominate artery; RCCA = right common carotid artery; LCCA = left common carotid artery; LSA = left subclavian artery; C = coarcted aortic arch; PA = pulmonary artery; H = haemorrhage.

stenosed part of the aortic arch, (*b*) at the bifurcation of the innominate artery, and (*c*) at the origin of the first branch of the right subclavian artery. The last was larger than the others and had spread into the adjacent connective tissue. Antemortem thrombus was present (*i*) in the left common carotid artery, extending from a point 2 cm. distal to its origin to its bifurcation some 3 cm. distally, (*ii*) in the right common carotid artery, extending from a point 1 cm. distal to its origin to its bifurcation 2·5 cm. distally and (*iii*) in the right subclavian artery, commencing at the origin of the vertebral artery and extending 4 cm. distally. No origin for emboli was found in the heart or aorta. The lungs showed generalized congestion. In the brain, a small area of softening was present in the right cerebral hemisphere superior to the insula. Thrombus was present in both internal carotids at their junction with the circle of Willis, the right being swollen suggesting antemortem thrombosis. Histology of the left common carotid artery and intracranial portions of both internal carotid arteries showed antemortem thrombus. The vessel walls showed no obvious disease.

Discussion

The case described was one of pulmonary hypertension with shunt reversal through the patent ductus arteriosus, associated with severe aortic coarctation, and complicated by multiple thromboses in the high tension side of the systemic arterial circulation.

The child appears to have lived for some weeks with occlusion of both common carotid vessels. Her ability to do so with no more than slight hemiparesis and a certain amount of irritability of temperament, was a tribute to her vertebral blood supply; her sudden death can presumably be ascribed to thrombosis of the right subclavian artery with involvement of its vertebral branch. The disturbance affecting the right forearm a few days before death, must have been caused by occlusion of the radial and ulnar arteries, or perhaps the brachial bifurcation. This could have been due to local thrombosis, or embolism from non-occluding right subclavian thrombus.

The cause of the vascular thrombosis is not readily apparent. No source of emboli was found at necropsy. Paradoxical emboli from a silent venous thrombosis would have had to move upstream and negotiate the coarctation in order to pass from the ductus to the carotid and right subclavian arteries: this seems unlikely.

Cross sections of thrombosed artery showed no abnormality of the vessel wall on microscopy. Certainty on this point, however, probably demands longitudinal sections as well, as shown by Moberg and Reinand (1956). They described the case of an infant with aortic coarctation proximal to a patent ductus arteriosus, in which thrombosis of the descending aorta occurred. Differential cyanosis was present as in our case, but could have been either peripheral in type, due to the thrombotic occlusion, or central, due to pulmonary hypertension and shunt reversal. Longitudinal sections of the aorta showed multiple transverse ruptures of microscopic size along its whole length, above and below the coarctation. Thrombosis probably arose at the site of minute intimal ulceration. Also, numerous haemorrhages, situated mainly in the media, were present throughout the aorta. The histology was considered to resemble that usually found in aortic dissecting aneurysms. The common association of the latter with coarctation of the aorta is well known, although rupture distal to the

stenosis is uncommon, tending usually to involve the ascending aorta.

The presence of adventitial haemorrhages at the proximal ends of the thrombosed vessels suggests that the pathogenesis might have been the same as in Moberg and Reinand's case in which there were haemorrhages in the aortic wall. Longitudinal sections, which might have shown transverse ruptures, were not made in our case.

No other cases of thrombosis of major systemic arteries complicating either coarctation of the aorta or pulmonary hypertension with reversed central shunt, have hitherto been reported.

Summary

The literature of carotid occlusive disease in childhood is briefly reviewed.

A case of multiple arterial occlusion, including bilateral common carotid thrombosis, in a child with congenital cardiovascular disease is described.

The aetiology of the thrombosis is speculatively discussed.

This case was under the care of Professor J. D. Hay and I would like to thank him for allowing me to report it. I wish also to thank Dr. J. S. Elwood for the autopsy report. They both very kindly provided the photographs.

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BOOK REVIEWS

ediatric Dermatology. By HENRY H. PERLMAN. (Pp. xii + 477; 203 figs. $18.00; 135s.) Chicago: The Year Book Publishers Inc. British distributors: Interscience Publishers Ltd.

Dr. Perlman, who is Clinical Professor of Pediatrics at Jefferson Medical College and Associate Professor at the University of Pennsylvania, is to be commended for his courage and industry in writing a textbook on dermatology. While he writes primarily for paediatricians, general practitioners and students, many dermatologists would find the book a useful addition to their bookshelves, for good books upon paediatric dermatology are rare. The latter would find added interest in a work based upon the principles of paediatric medicine, with a secondary approach to dermatology. The author's wide experience in two specialties and in pharmacology gives him an unusual breadth of approach which is reflected in the excellent chapters on physical examination and history-taking that few of us can hope to emulate. His wisdom in advocating the simpler and well tried remedies is a fresh current of common sense throughout the chapters on treatment and topical remedies.

There follows some thought provoking observations on the skin hygiene of the newly-born and only aesthetic objections can be raised against the idea of leaving more to nature and not approaching godliness via soap and water unless the infant has a normal skin.

Inevitably an experienced dermatologist can find a few weak spots as critical reviewers find in our own writings. We found some confusion in the account of subcutaneous induration of the new born. Whilst a low olein content of the subcutaneous fat may lead to the formation of fatty crystals of a higher melting point and a granulomatous reaction to their presence, which we regard as the specific basis of sclerema neonatorum, subcutaneous fat necrosis in infants or adults is not related to the olein content and has a banal histology. Dr. A. M. H. Gray deserved a reference here.

No mention is made of agammaglobulinaemia which has been recorded in cases of dermatitis gangraenosa and probably accounts for the infant's grave susceptibility to infection. Injections of gamma globulin may be life saving in some cases.

Although the old and little used arsenical medication is included in the treatment of dermatitis herpetiformis, the more effective drug diamino-diphenylsulphone is omitted from the schedule of treatment. A better name for granuloma pyogenicum is granuloma telangiectaticum, for whereas the abundance of vascular tissue is obvious, the pyogenic factor can rarely be demonstrated.

It is stated that aphthous stomatitis is caused by the herpes virus. Harvey Blank and others have failed to confirm this aetiology.

Surely too much stress is put upon the treatment of strawberry marks and cavernous haemangiomata, most of which may more safely be left for the usual spontaneous resolution.

Lest we damn, by faint praise, in finding minor points of disagreement, which may be controversial in any case, let us add that this is a good book; the standard of printing, illustrations and binding is of the highest. It is almost pure American with perhaps too few references to the outside world literature. However, the standard of dermatological knowledge and progress is probably the highest in the U.S.A., and it merely remains to one who has suffered the pangs of book-birth to congratulate the author.

Notes on Infant Feeding. By STANLEY GRAHAM and ROBERT A. SHANKS. (Pp. 76. 4s. 6d.) Edinburgh: E. and S. Livingstone Ltd. 1960.

A hearty welcome can be given to another edition of this little book at the very reasonable price of 4s. 6d. It contains much useful advice and information which is concisely given and it can be recommended equally to the student and young doctor. Some of it seems a little old-fashioned and the Sassenach baby, for instance, nowadays seems to double his weight well before the six months the authors allow.

Pathology of Infancy and Childhood. By AGNES R. MACGREGOR. (Pp. 631; 388 figs. 75s.) Edinburgh and London: E. & S. Livingstone Ltd. 1960.

Agnes Macgregor of international renown is one of the foremost pioneers of paediatric pathology. Her colleagues in the United Kingdom especially owe much to her influence and this book places them further in her debt. As she says in the preface it is not intended primarily for those familiar with the subject but for those pathologists who deal only occasionally with paediatric problems. As such it fills a long-felt gap in the literature.

About one third is taken up with the perinatal period and congenital malformations. The remainder is devoted to the infective, degenerative, metabolic and neoplastic diseases which occur in later infancy and childhood. There are also short but extremely valuable chapters on blood diseases, accidental injuries and poisons.

Most of these subjects are dealt with inadequately in general pathological texts, but here they are given their proper emphasis. For this reason paediatricians and paediatric surgeons will find this an extremely useful book. The pathological aspects of almost all their clinical problems are described in one volume of convenient size.

Of particular interest to the occasional paediatric pathologist are the observations on sudden unexpected

deaths, the advice on perinatal autopsy technique and the tables of normal measurements found at the end of the book.

The text is well set out in clear print and is not interrupted by unnecessary detail. Important references are given at the end of each chapter and there is a complete index at the end of the book. The illustrations are well chosen and clear and those of the cardiac malformations and the whole lung slices are of particular merit.

This book should be included in the libraries of all paediatric and pathological departments.

Le Syndrome D'Ellis-Van Creveld. Une forme de dysplasie chondro-ectodermique. By L. DAYER. (Pp. iv + 59; 18 figs., 4 tables. sFr. 12.50.) Basel and New York: S. Karger. 1960.

The author has reviewed 33 published cases of the syndrome (ectodermal dysplasia, polydactyly, chondrodysplasia and congenital morbus cordis) and has added four personal observations showing either the complete syndrome or variants, e.g. punctate epiphyseal dysplasia. Of a total of 36 cases regarded as examples of the syndrome, 11 showed parental consanguinity and 10 belonged to five sibships, including one pair of dizygotic twins. Recessive inheritance which was postulated when the three original cases were reported in the *Archives of Disease in Childhood* in 1940 appears to be confirmed. Of the 36 cases reviewed, 18 were boys and 18 girls. The condition has now been described in children of Jewish, English, Dutch, French, Italian, Swiss, Turkish, Algerian, Tunisian, Anglo-Irish, coloured American and mixed parentage. Of the various features of the syndrome, congenital morbus cordis seems to be the least constant, being present in only 20 cases, and ectodermal defects the most constant. The author points out that the syndrome is one of a number in which chondral and ectodermal dysplasias coexist, and that transitional types occur.

Child Development: An International Method Study. Ed. A. HOTTINGER and H. BERGER. Modern Problems in Pediatrics, V. Supplement to Annales Paediatrici. (Pp. ix + 237; 20 figs. sFr. 50.-.) Basel/New York: S. Kargar A.G. 1960.

The reviewer is in the embarrassing position of being asked to write a testimonial for a favourite son and seven grandchildren. Nevertheless, he feels gratified at being able to commend this quite remarkable achievement of an international study which, fostered by the International Children's Centre in Paris, derived from the Child Study Centre in London, a product of collaboration between the University's Institutes of Education and Child Health. Nine chapters set out the history of the coordinated studies, the general considerations and lines of work, followed by three important sections on the social, psychological and physical (somatic) investigations. A chapter on the special aspects of the problem in under-developed countries, and another on the effects of malnutrition on growth, takes the study out of Europe into West and East Africa. Dr. Faulkner's own, slightly different, present work in Louisville, Kentucky, marks the spread of the collaboration to the New World. An appendix of 100 pages gives some idea of the complexity of the data collected by reproducing the various forms in use. A study of these shows how necessary is the final chapter in the body of the volume on the practical problem of recording and analysing the completed schedules. Indeed the difficulties of getting corresponding growth studies started in eight centres seem small compared with the rapidly growing problem of what to do with the material collected. This is a valuable contribution to paediatric literature and an essential guide book for those embarking on growth and development studies. The whole text is in English, well presented and the volume beautifully produced. Professor Robert Debré contributes a characteristically charming foreword.

Kinderheilkunde: Diagnostik-Therapie, Prophylaxe. By ERWIN GRUNDLER and GERHARD SEIGE. (Pp. 846, 848 figures. DM. 29.-.) Stuttgart: Hippokrates-Verlag. 1960.

This is a beautifully bound and printed synopsis of children's diseases, written in a telegraphic style. The synopsis includes a little on normal development, gives physiological values, describes infant feeding and the various immunizing procedures before the systematic description of the illnesses in childhood. It ends with a chapter of over 100 pages which gives an alphabetical list of all drugs used at present (and in the past), together with all the available proprietary preparations, giving doses, methods of administration, indications, mode of action and side-effects. For a synopsis the book is too voluminous. It would gain a great deal by drastic pruning of out-dated material. For example, it treats syphilis with arsenic and bismuth, advises deep x-ray therapy for hyperplasia of the thymus in infants and devotes a chapter to thymus lymphaticus. On the aetiology of infantile diarrhoea the concepts of exudative and neuropathic diathesis are still maintained and its dietary management is equally antiquated. Bed-wetting should not be treated by corporal punishment, but the example of good children should be constantly kept in front of the offender; favourite foods and other pleasures should be denied until the offenders mend their ways. One could give a long list of such quaint ideas. In summary this book includes all that is new without having discarded much from the past which is no longer tenable.

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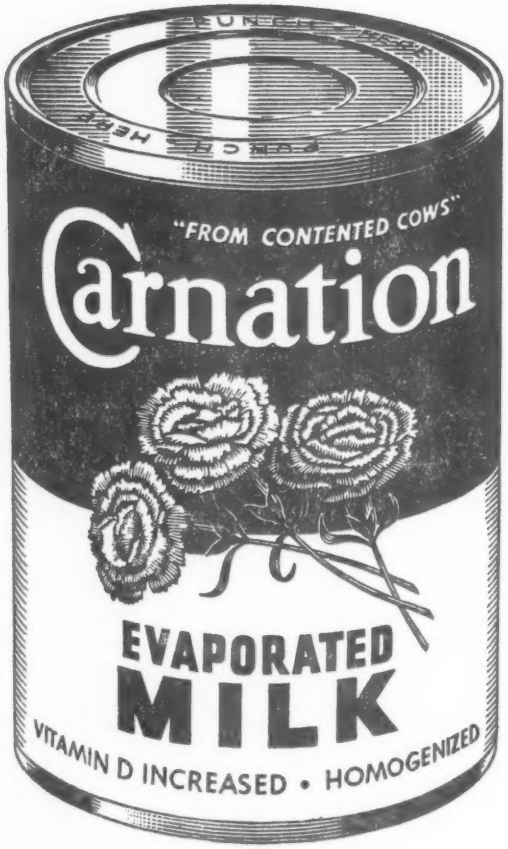

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